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COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES

FIELD OF INVENTION

DPSA1
The present invention relates to novel compounds, compositions containing them, and their use for treating medical disorders resulting from a deficiency in growth hormone.

10 BACKGROUND OF THE INVENTION

Growth hormone is a hormone which stimulates growth of all tissues capable of growing. In addition, growth hormone is known to have a number of effects on metabolic processes, e.g., stimulation of protein synthesis and free fatty acid mobilisation and to cause a switch in energy metabolism from carbohydrate to fatty acid metabolism. Deficiency in growth hormone can result in a number of severe medical disorders, e.g., dwarfism.

Growth hormone is released from the pituitary. The release is under tight control of
20 a number of hormones and neurotransmitters either directly or indirectly. Growth hormone release can be stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin. In both cases the hormones are released from the hypothalamus but their action is mediated primarily via specific receptors located in the pituitary. Other compounds which stimulate the release of growth hormone from
25 the pituitary have also been described. For example arginine, L-3,4-dihydroxyphenylalanine (L-Dopa), glucagon, vasopressin, PACAP (pituitary adenylyl cyclase activating peptide), muscarinic receptor agonists and a synthetic hexapeptide, GHRP (growth hormone releasing peptide) release endogenous growth hormone either by a direct effect on the pituitary or by affecting the release
30 of GHRH and/or somatostatin from the hypothalamus.

In disorders or conditions where increased levels of growth hormone is desired, the protein nature of growth hormone makes anything but parenteral administration non-viable. Furthermore, other directly acting natural secretagogues, e.g., GHRH and PACAP, are longer polypeptides for which reason parenteral administration is
5 preferred.

The use of certain compounds for increasing the levels of growth hormone in mammals has previously been proposed, e.g. in EP 18 072, EP 83 864, WO 89/07110, WO 89/01711, WO 89/10933, WO 88/9780, WO 83/02272, WO
10 91/18016, WO 92/01711, WO 93/04081, WO 9517422, WO 9517423 and WO 9514666.

The composition of growth hormone releasing compounds is important for their growth hormone releasing potency as well as their bioavailability. It is therefore the
15 object of the present invention to provide compounds of peptide mimetic nature with growth hormone releasing properties which have improved properties relative to known compounds of this type.

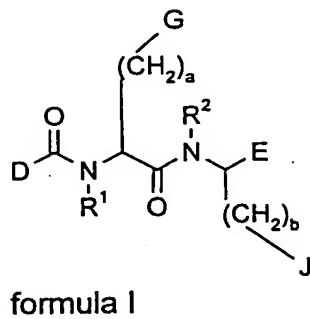
SUMMARY OF THE INVENTION

20 In accordance with the present invention there is provided compounds which act directly on the pituitary cells under normal experimental conditions in vitro to release growth hormone therefrom.

25 These growth hormone releasing compounds can be utilized in vitro as unique research tools for understanding, inter alia, how growth hormone secretion is regulated at the pituitary level.

Moreover, the growth hormone releasing compounds of the present invention can
30 also be administered in vivo to increase growth hormone release.

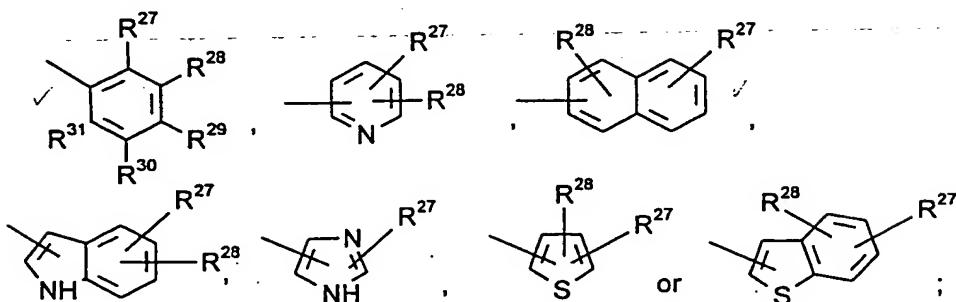
Accordingly, the present invention relates to a compound of the general formula I



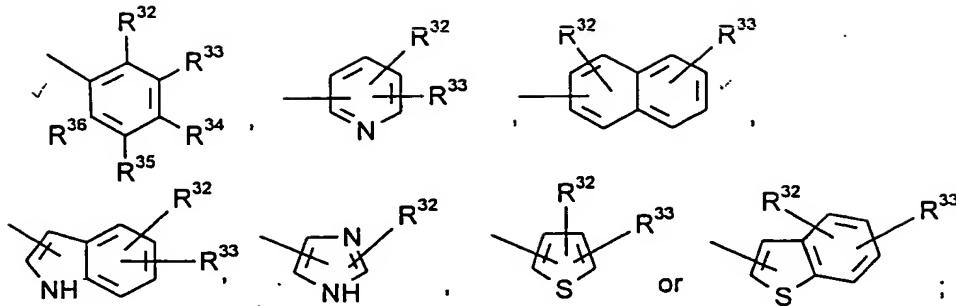
5

wherein

- 10 R¹ and R² are independently hydrogen, or C₁₋₆-alkyl optionally substituted with aryl;
- a and b are independently 1 or 2;
- 15 G is hydrogen, -O-(CH₂)_k-R²⁷,



J is hydrogen, -O-(CH₂)_l-R³²,

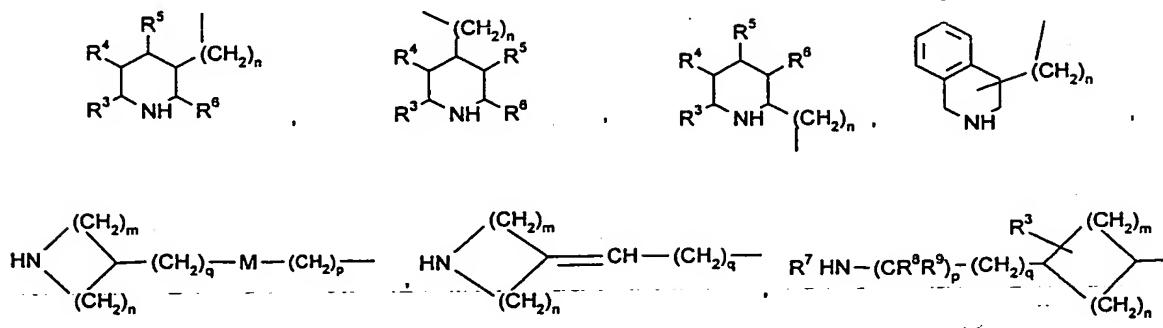


wherein R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵ and R³⁶ independently are hydrogen, halogen, aryl, C₁₋₆-alkyl or C₁₋₆-alkoxy;

5 k and l are independently 0, 1 or 2;

D is

10



15

wherein R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are independently hydrogen or C₁₋₆-alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

n, m and q are independently 0, 1, 2, or 3;

p is 0 or 1;

20 M is -CR¹¹=CR^{11a}-, aryl, -O-, or -S-;

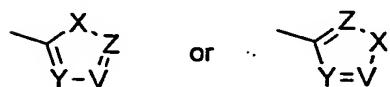
R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with aryl;

with the proviso that at least one of R³, R⁴, R⁵ and R⁶ is different from hydrogen,

when E is

- CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},
- CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴,
- (CH₂)_v-NR¹²-CO-NR¹³R¹⁴,

5



wherein

X is -N(R¹⁵)-, -O- or -S-,

10 V is -C(R¹⁶)= or -N=,

Y is -C(R¹⁷)= or -N=,

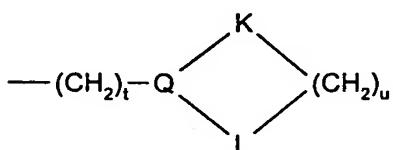
Z is -C(R¹⁸)= or -N=,

R¹⁵ is hydrogen or C₁₋₆-alkyl optionally substituted with aryl,

15 R¹⁶, R¹⁷ and R¹⁸ independently are hydrogen, -COOR¹⁹, -CONR²⁰R²¹, -(CH₂)_wNR²⁰R²¹, -(CH₂)_wOR¹⁹, -(CH₂)_wR¹⁹ or halogen;

R¹², R¹³, R¹⁹, R²⁰ and R²¹ independently are hydrogen or C₁₋₆-alkyl optionally substituted with halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyloxy or aryl,

or R¹³ is



25 wherein

Q is -CH< or -N<,

K and L are independently -CH₂- , -CO-, -O-, -S-, -NR²⁶- or a valence bond, where R²⁶ is hydrogen or C₁₋₆-alkyl;

t and u are independently 0, 1, 2, 3 or 4;

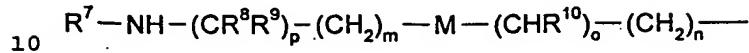
R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆-alkyl;

5 v and w are independently 0, 1, 2 or 3;

D is



wherein R⁷, R⁸, R⁹ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

R⁷ and R⁸ or R⁷ and R⁹ or R⁸ and R⁹ optionally forming -(CH₂)_iU-(CH₂)_j-, wherein i

15 and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

n and m are independently 0, 1, 2, or 3;

o and p are independently 0 or 1;

M is -CR¹¹=CR^{11a}-, aryl, -O-, or -S-;

R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with

20 aryl,

when E is

-CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},

25 -(CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴ or

-(CH₂)_v-NR¹²-CO-NR¹³R¹⁴,

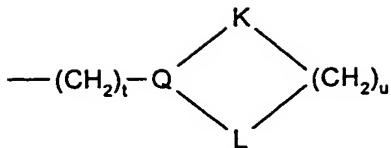
wherein

R¹² and R¹³ independently are hydrogen or

30 C₁₋₆-alkyl optionally substituted with halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃,

hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyloxy or aryl;

or R¹³ is



wherein

- 5 Q is -CH< or -N<;
K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond,
where R²⁶ is hydrogen or C₁₋₆ alkyl;
t and u are independently 0, 1, 2, 3 or 4;
R^{13a} is C₁₋₆ alkyl substituted with aryl;
- 10 R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆ alkyl;
v and w are independently 0, 1, 2 or 3;
- 15 or a pharmaceutically acceptable salt thereof, and the compounds of formula I
comprise any optical isomers thereof, in the form of separated, pure or partially
purified optical isomers or racemic mixtures thereof.

In the compound of the above formula I D is preferably

- 20 3-(1-aminoethyl)phenyl, 4-amino-4-ethylhex-1-enyl, (1E)-2-(azetidin-3-yl)ethenyl,
piperidin-4-ylidenyl,
2-methylpiperidin-4-yl, 2-methylpiperidin-3-yl, 2-methylpiperidin-5-yl,
(1,2,3,4-tetrahydroisoquinolin-1-yl)methyl, 4-aminocyclohexyl,
2-piperidylmethoxymethyl, 4-piperidyloxymethyl,
- 25 2-(2-amino-2-methylpropyl)cyclopropyl, (((2R)-pyrrolidin-2-yl)methoxy)methyl,
(1E)-4-amino-1-benzyl-4-methylpent-1-enyl, (1E)-4-amino-4-methylpent-1-enyl,
(2-amino-2-methylpropoxy)methyl, (2S)-(2-pyrrolidinyl)methoxymethyl, (2R)-(2-pyrrolidinyl)methoxymethyl, (1E)-4-amino-2,4-dimethylpent-1-enyl, (1E)-4-methyl-4-(methylamino)pent-1-enyl, (1Z)-4-amino-4-methylpent-1-enyl,

(1E)-4-((2R)-2-hydroxypropylamino)-4-methylpent-1-enyl,
 (2-aminobutoxy)methyl, 3-(1-aminoethyl)phenyl, 3-aminomethylphenyl, 3-(1-amino-1-methylethyl)phenyl, 2-(1-amino cyclopropyl)ethenyl, 3-(1-aminocyclobutyl)-1-propenyl, 3-(1-aminocyclopropyl)-1-propenyl or 2-(1-amino
 5 cyclobutyl)ethenyl.

In the compound of the above formula I E is preferably methylcarbamoyl,
 ethylcarbamoyl, N,N-dimethylcarbamoyl,
 2-methoxyethylcarbamoyl, (2S)-2-hydroxypropylcarbamoyl,
 10 (2R)-2-hydroxypropylcarbamoyl, (cyclopropylmethyl)carbamoyl, (2-(acetoxy)-2-methylpropyl)carbamoyl, phenylethylcarbamoyl, 4-pyridylcarbamoyl,
 (3-acetoxypropyl)carbamoyl, (3-hydroxypropyl)carbamoyl,
 methylsulfonylaminomethyl, ((tetrahydrofuran-2-yl)methyl)carbamoyl, 3-cyclopropylthioureido, N-methyl-N-(methylsulfonylamino)methyl, (2,2,2-
 15 trifluoroethyl)carbamoyl, cyclopropylcarbamoyl,
 ((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl,
 3-methyl-1,2,4-oxadiazol-5-yl, methylsulfonylaminomethyl, 2,2-dimethyl-3-hydroxypropylcarbamoyl, 2-(1-methylpyrrolidine-2-yl)ethylcarbamoyl, N-methyl-N-(3-(dimethylamino)propyl)carbamoyl, N-(N,N-dimethylcarbamoyl)-N-
 20 methylcarbamoyl, N-(carbamoylmethyl)carbamoyl or 3-cyclopropylthioureido.

In the compound of the above formula I G is preferably
 2-naphthyl, 1-naphthyl, 2-benzyloxy, biphenyl-4-yl or 3-benzo[b]thiophenyl, 4-methoxyphenyl, 2,3,4,5,6-pentafluorophenyl.

25

In the compound of the above formula I J is preferably
 phenyl, 2-fluorophenyl, 4-fluorophenyl, 4-iodophenyl, 3,4-difluorophenyl
 2-thienyl, 4-methoxyphenyl, 2,3,4,5,6-pentafluorophenyl, 2-naphthyl or 1-naphthyl.

30

In the compound of the above formula I R¹ is preferably

hydrogen, methyl or ethyl.

More preferably R¹ is hydrogen, or methyl.

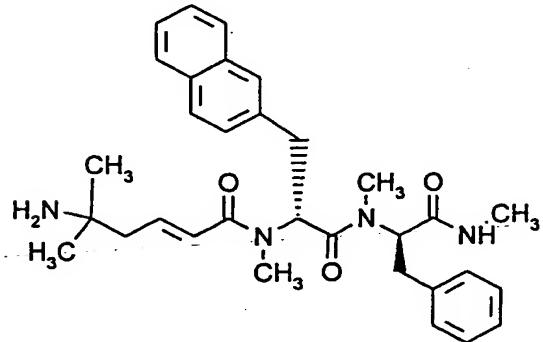
5 In the compound of the above formula I R² is preferably hydrogen, methyl or ethyl.

In the compound of the above formula I a is preferably 1.

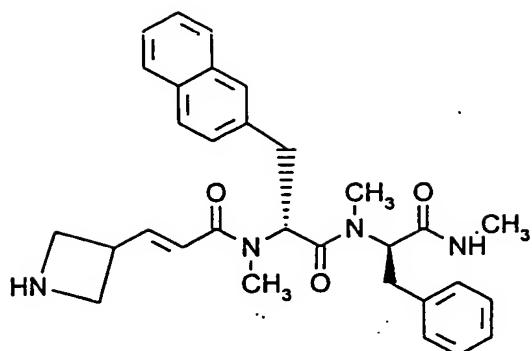
10 In the compound of the above formula I b is preferably 1.

Preferred compounds of the invention are:

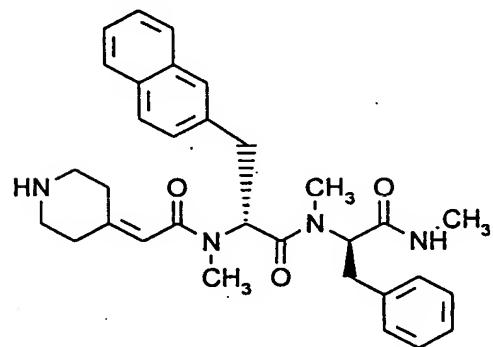
15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



20 (2E)-3-(3-Azetidinyl)acrylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

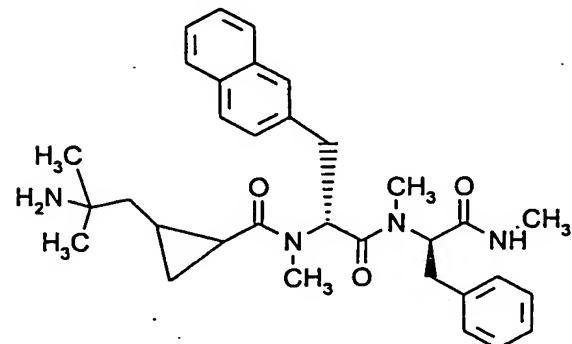


2-(Piperidin-4-ylidene)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



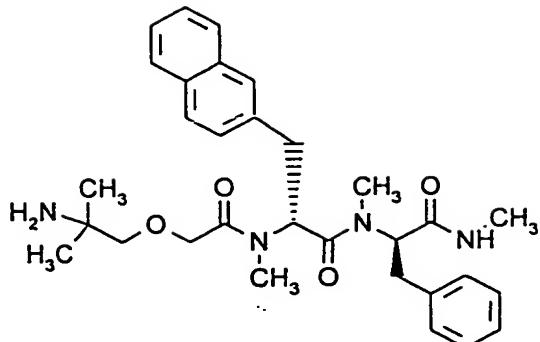
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2-(2-Amino-2-methylpropyl)cyclopropanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

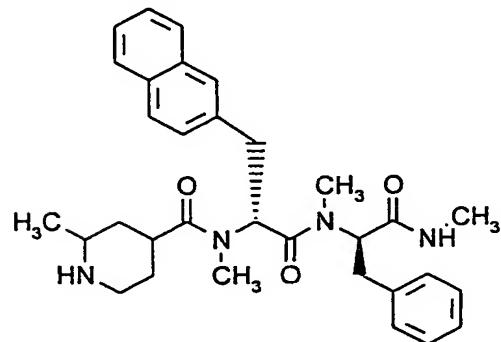


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2-(2-Amino-2-methylpropoxy)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

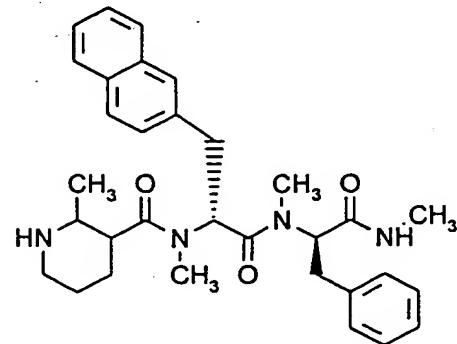


2-Methylpiperidine-4-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



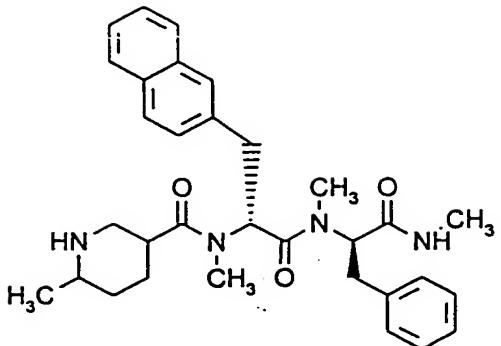
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2-Methylpiperidine-3-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

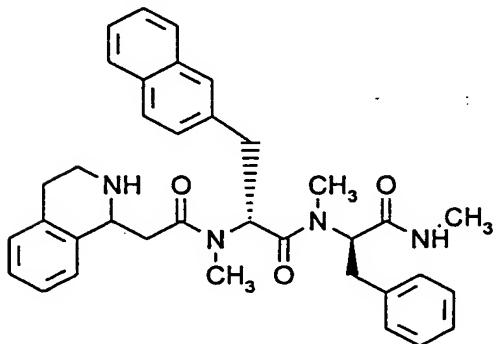


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2-Methylpiperidine-5-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

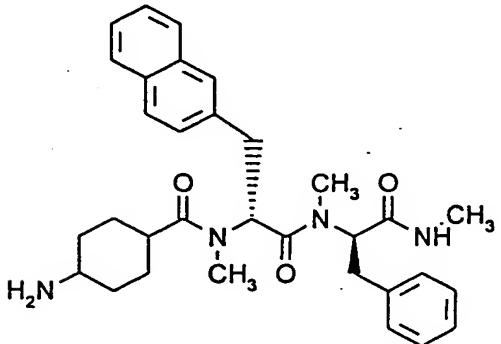


2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



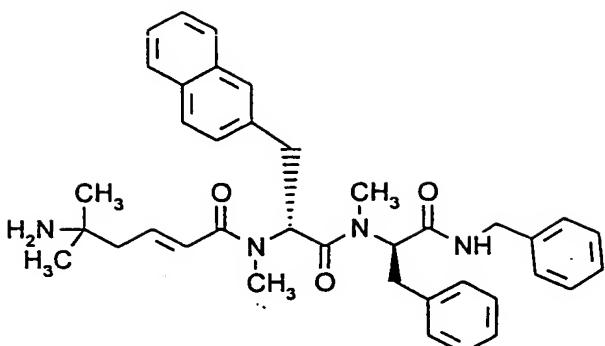
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4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

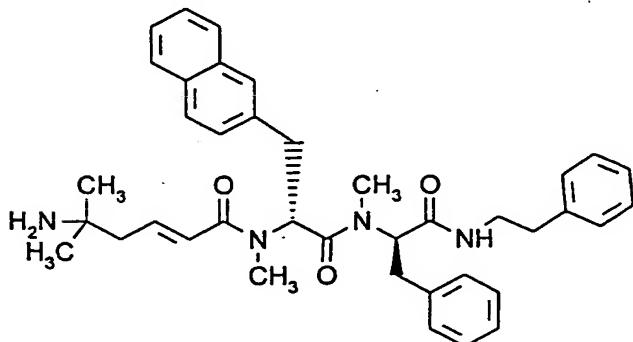


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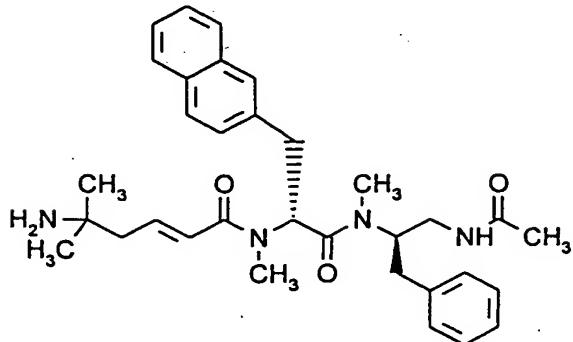
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(benzylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



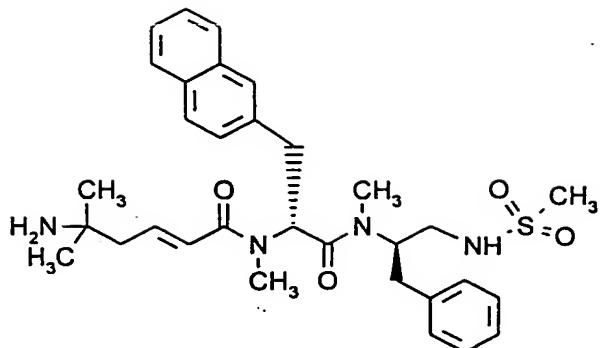
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(phenethylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



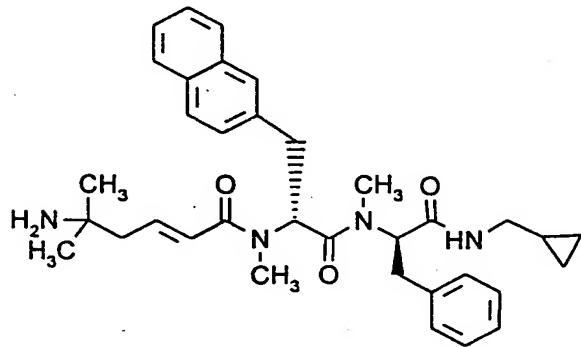
5 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-(acetylaminomethyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide:



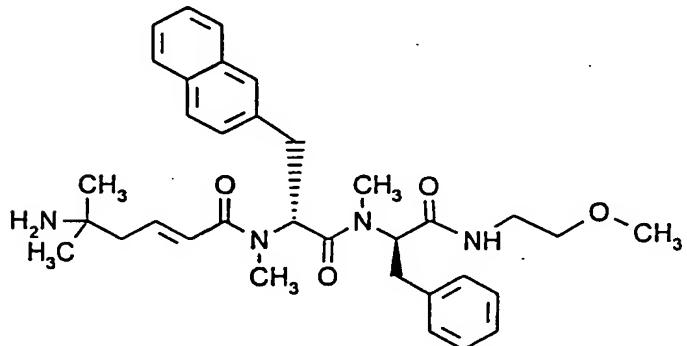
10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-1-(methylsulfonylaminomethyl)-2-phenylethyl]carbamoyl}-2-(2-naphthyl)ethyl)amide:



5 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-((cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

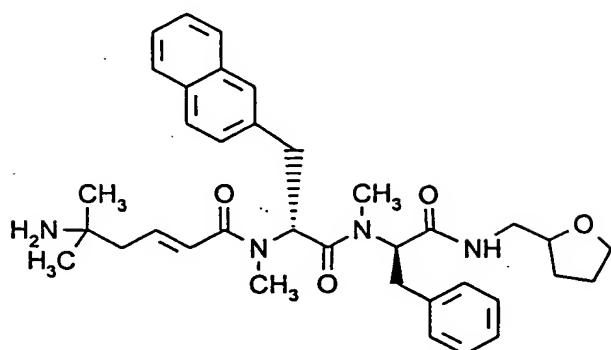


10 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-(2-methoxyethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



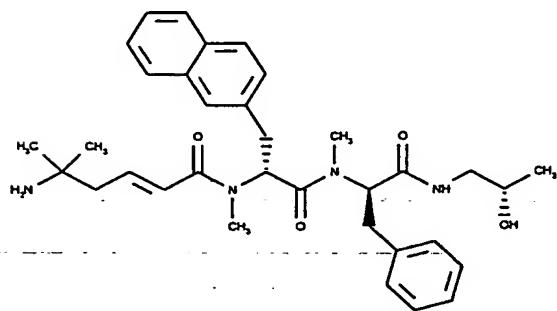
15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((N-tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethylcarbamoyl)-2-(2-naphthyl)ethylcarbamoyl-N-methylamide:

naphthyl)ethyl)amide:



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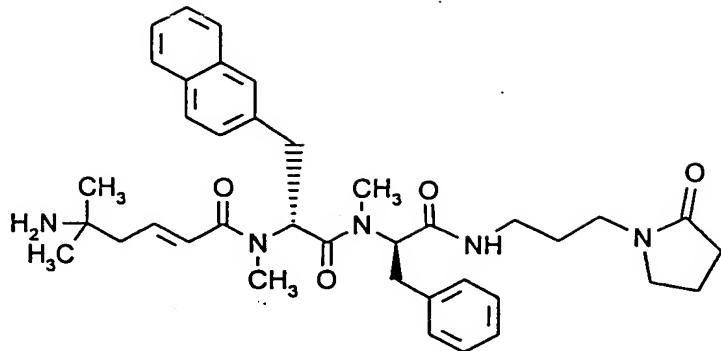
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-(2S)-2-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



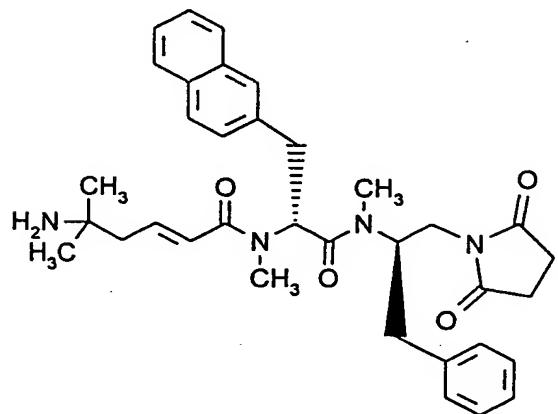
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(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(N-(3-(2-oxopyrrolidin-1-yl)propyl)carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

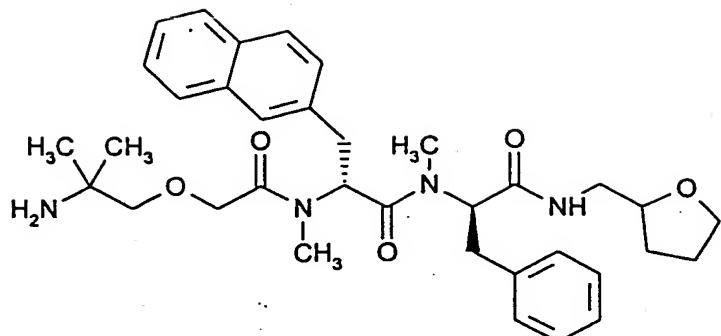
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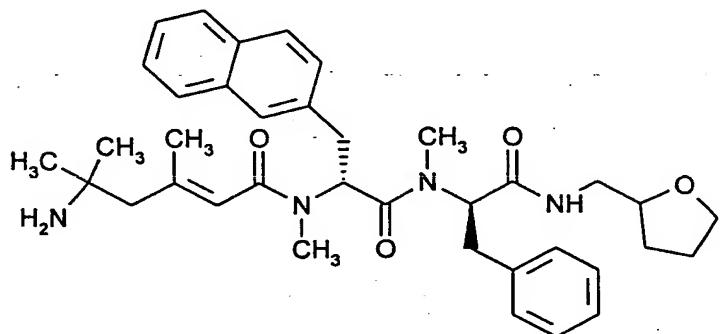
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-((2,5-dioxopyrrolidine-
5-yl)methyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-
methylamide:



10 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-N-methyl-3-(2-
naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-
propionamide:

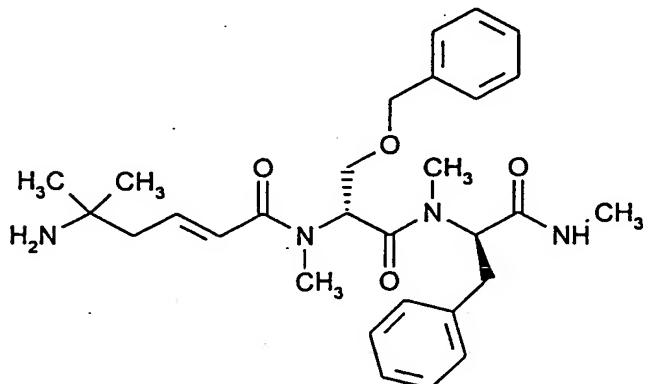


(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((2-tetrahydrofuranyl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

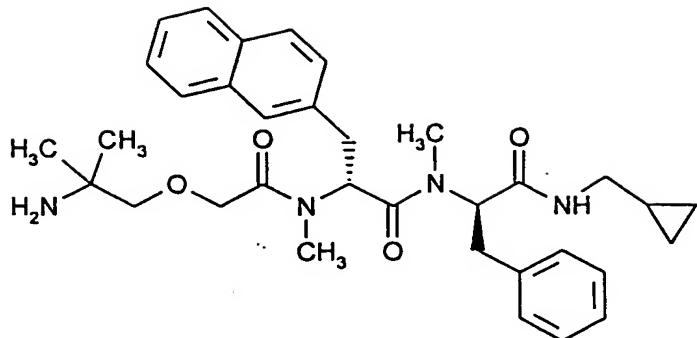


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(2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylamide:

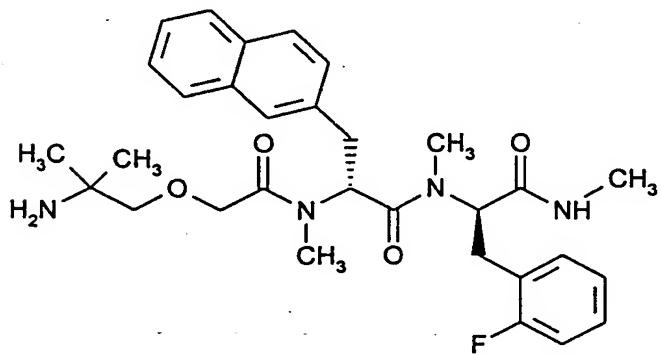


10 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-1-(cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)-propionamide:

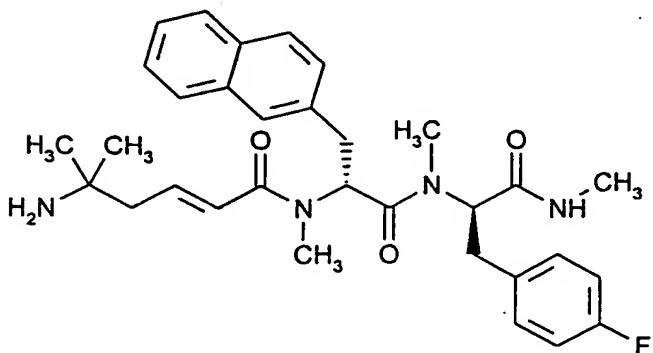


(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:

5

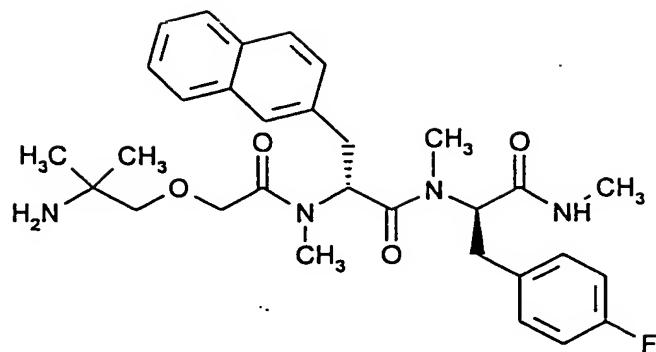


(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

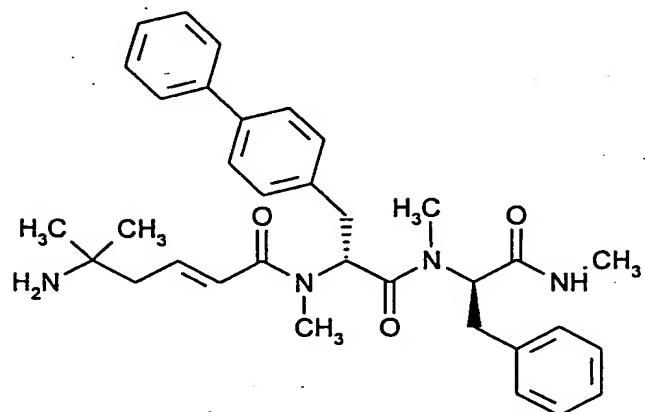


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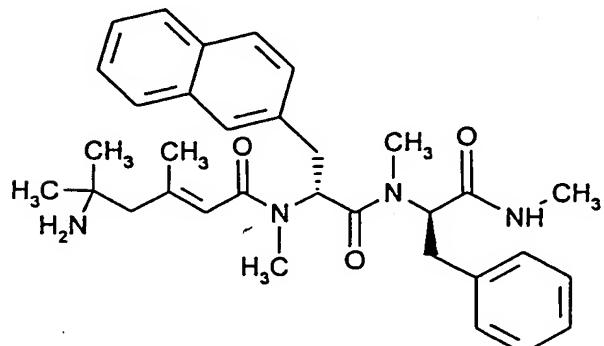
(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)N-methylamino)-N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:



(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide:

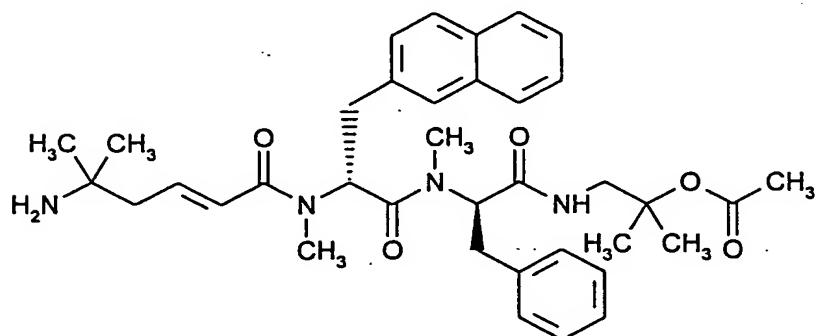


(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



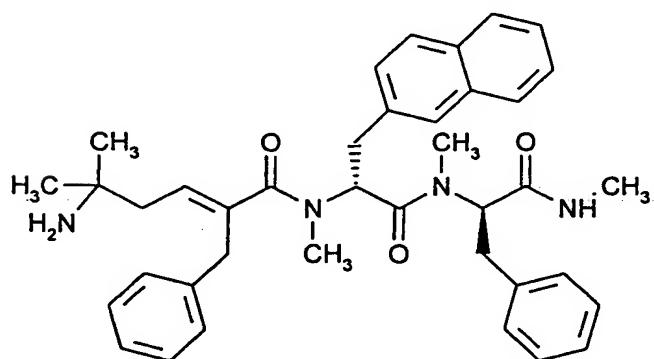
2-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:

5

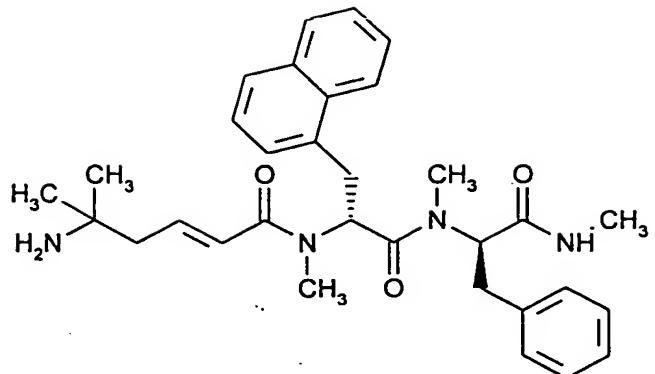


(2E)-5-Amino-2-benzyl-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

10

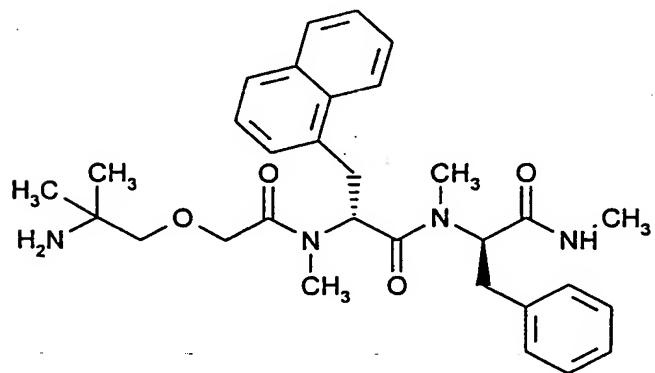


(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide:

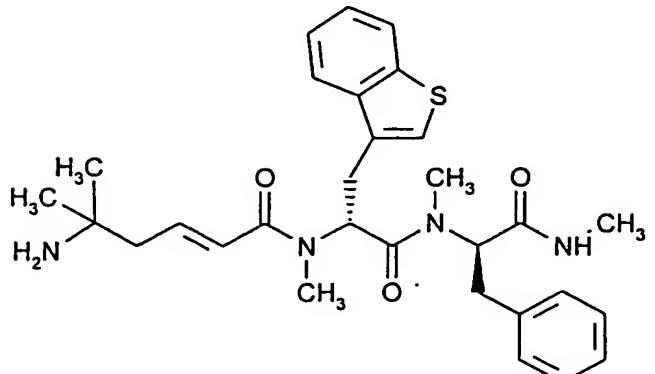


(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide:

5



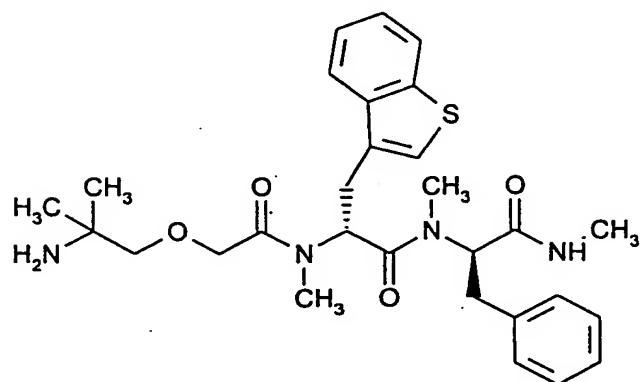
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-(benzo[b]thiophen-3-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)N-methylamide:



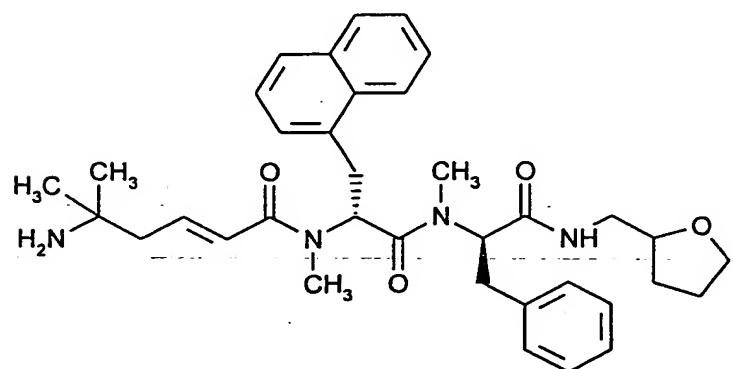
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(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-3-(benzo[b]thio-

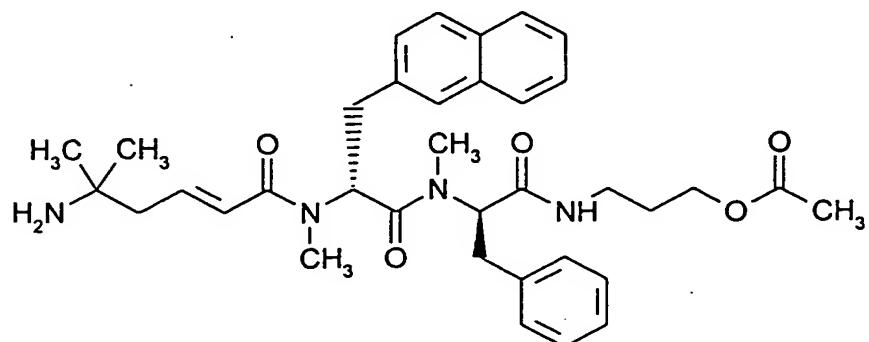
phen-3-yl)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)propionamide:



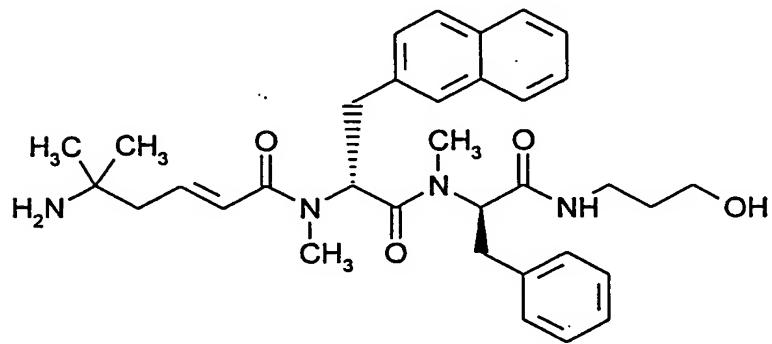
5 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide:



10 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



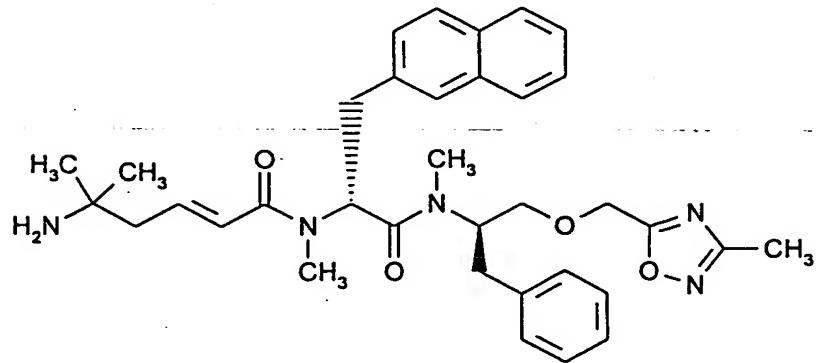
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



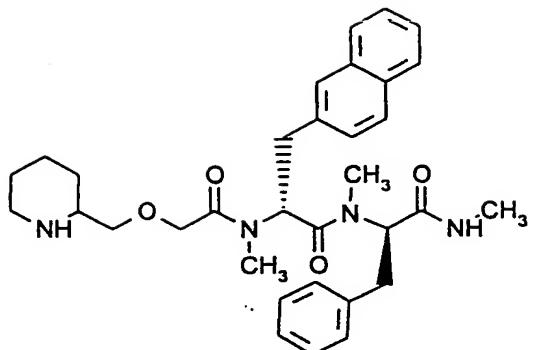
5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

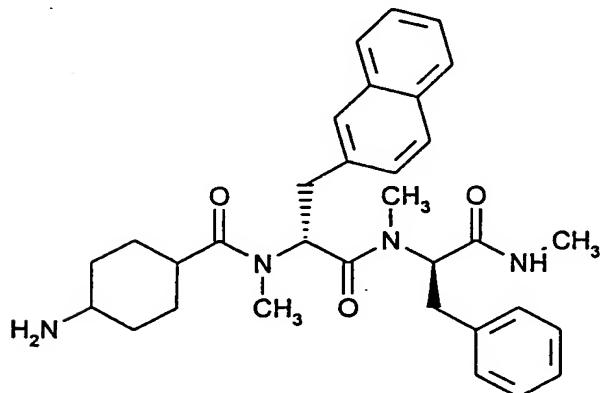
10



N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(2-piperidinyl)methoxy]acetyl}amino)-3-(2-naphthyl)propionamide:

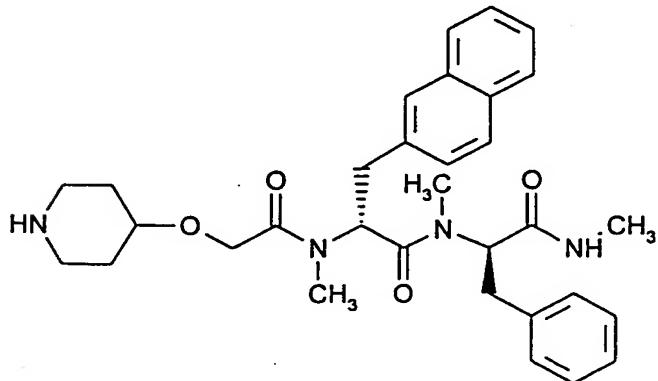


4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N- methyl-N-(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl]-2-(2-naphthyl)ethyl)amide:



5

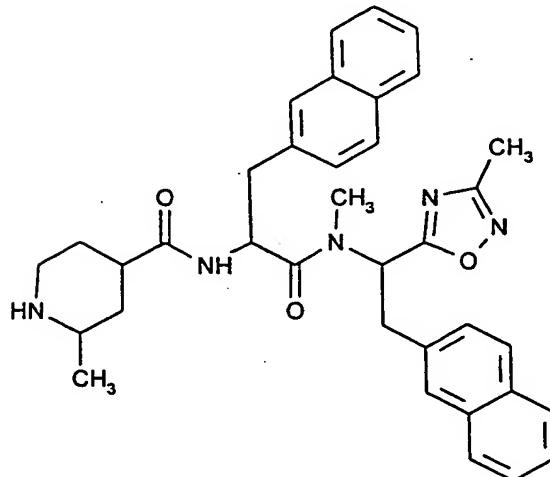
(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(piperidin-4-yloxy}acetyl]amino)-3-(2naphthyl)propionamide:



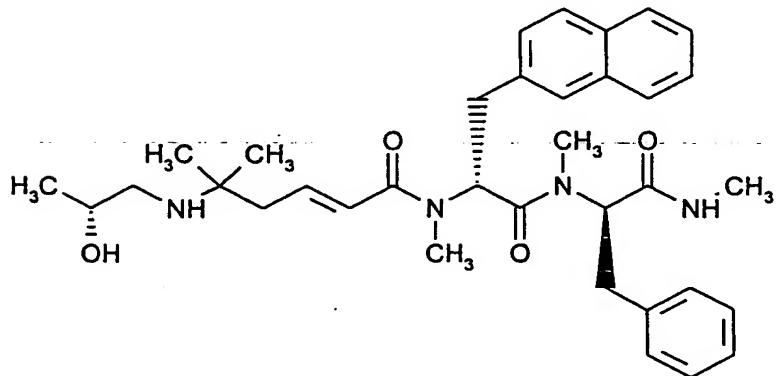
10

2-Methyl-piperidine-4-carboxylic acid N-{1-[N-methyl-N-(1-(3-methyl-1,2,4-

oxadiazol-5-yl)-2-(2-naphthyl)ethyl)carbamoyl]-2-(2-naphthyl)ethyl} amide;

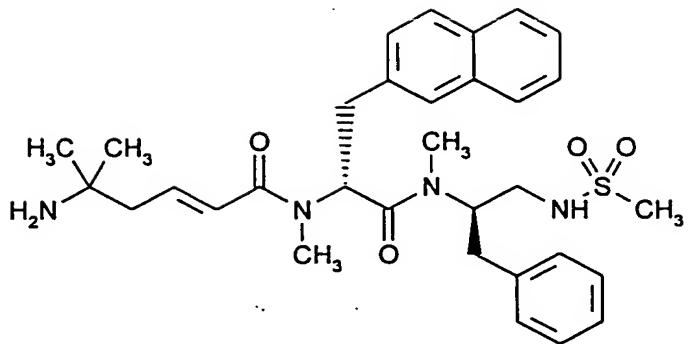


(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-Hydroxypropylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;

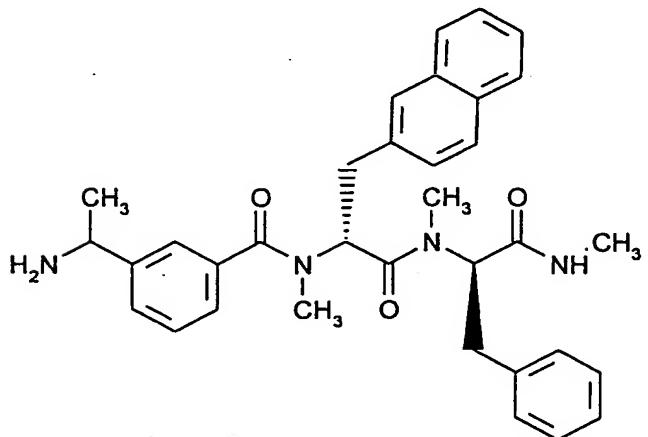


10 (2E)-5-Amino-N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-5-methyl-N-methylhex-2-enamide;

T00075555
5
A
O
D
B
E



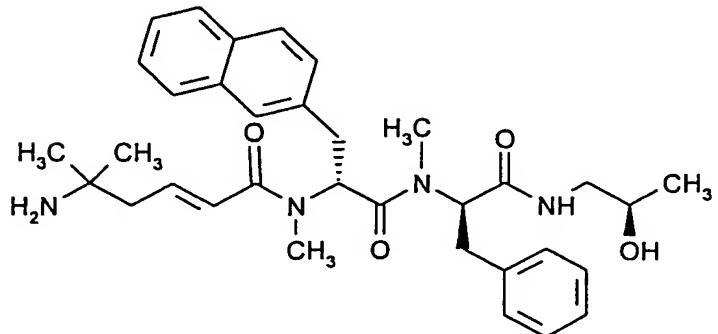
3-(1-Aminoethyl)benzoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



5

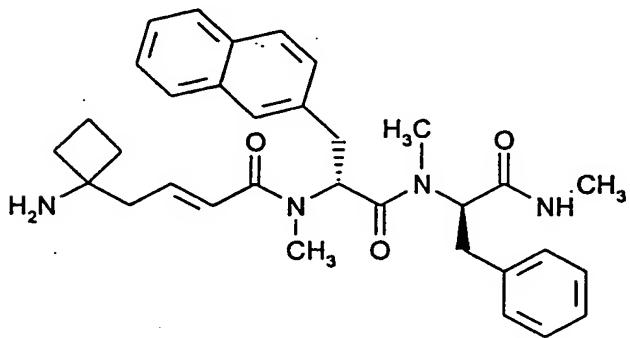
5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2R)-2-hydroxypropylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide:

10

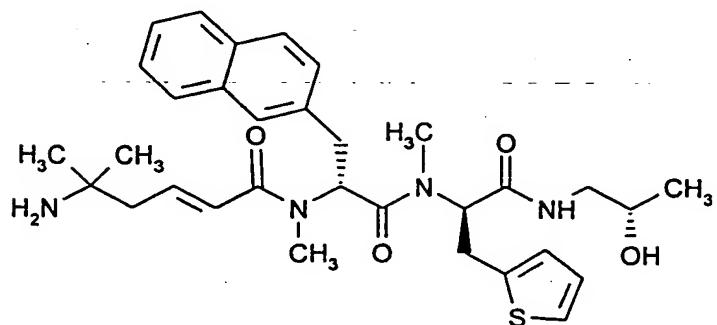


(4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-(((1R)-1-(1-methylcarbamoyl-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide:

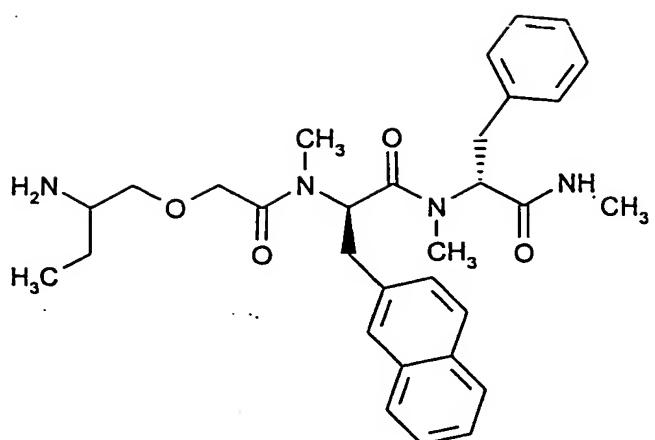
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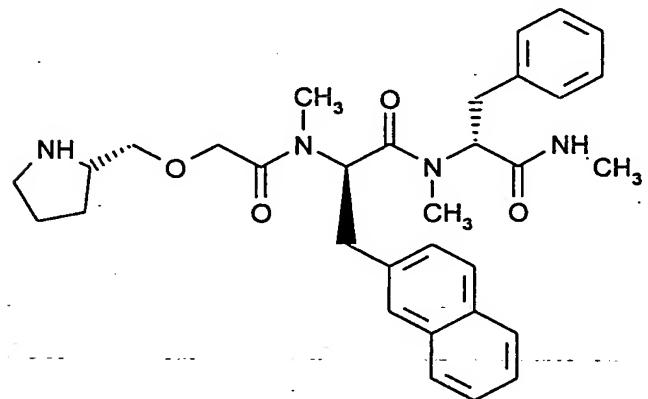
5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(2-thienyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.



(2R)-2-(N-[(2R)-2-(N-[(2-Aminobutoxy)acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide:

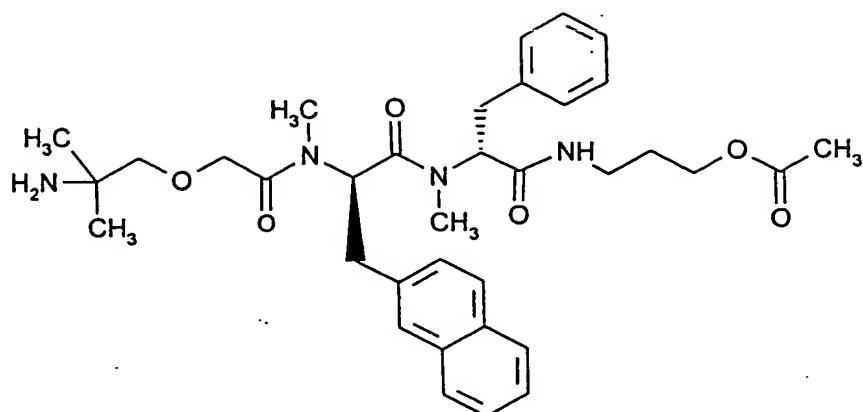


(2R)-N-Methyl-2-(N-methyl-N-((2R)-2-(N-methyl-N-(((2S)-pyrrolidin-2-yl)methoxy)acetyl)amino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionamide

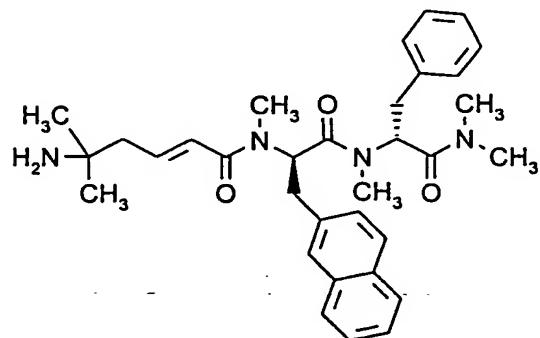


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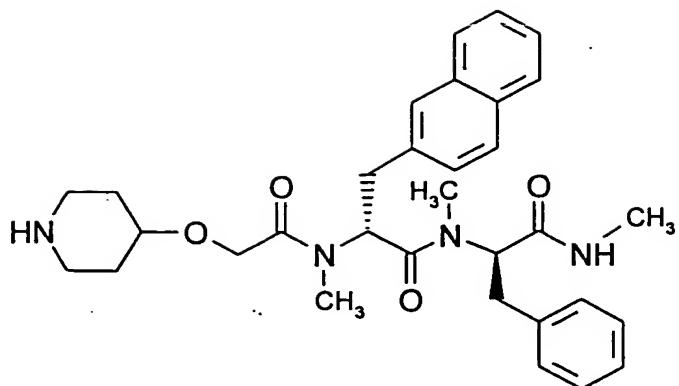
3-((2R)-2-(N-((2R)-2-(N-((2Amino-2-methylpropoxy)acetyl)amino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate



5 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

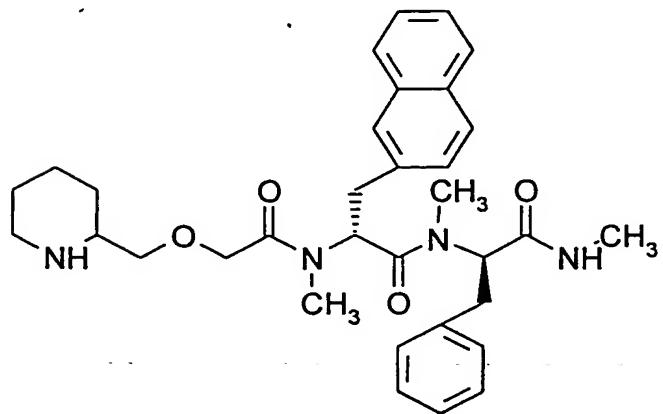


(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(piperidin-4-yloxy]acetyl]amino)-3-(2-naphthyl) propionamide

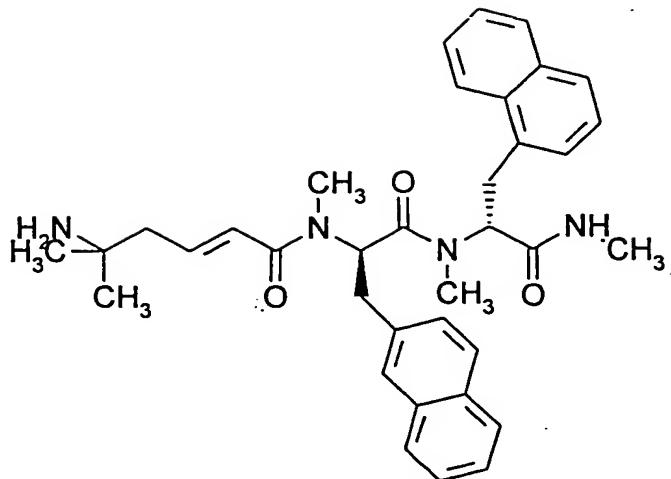


N-Methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(2-piperidinyl)methoxy]acetyl)amino)-3-(2-naphthyl)propinamide

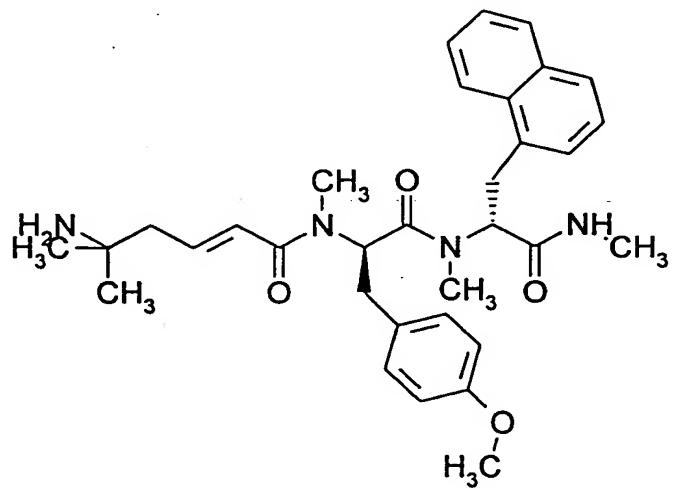
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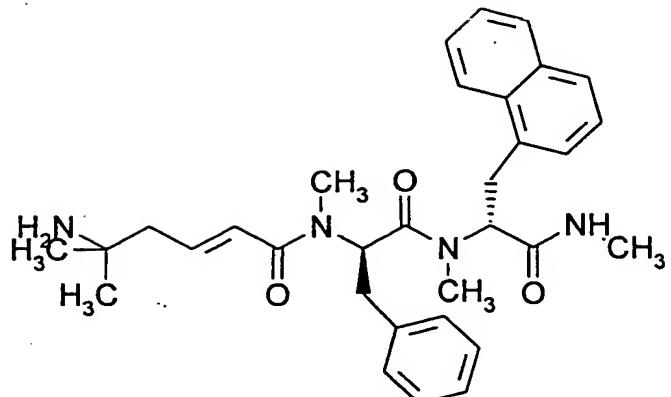
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1*R*)-1-{N-[(1*R*)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)amide:



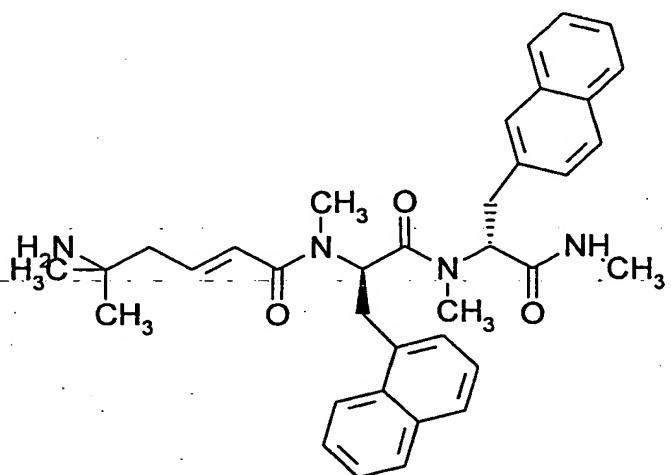
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[((1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



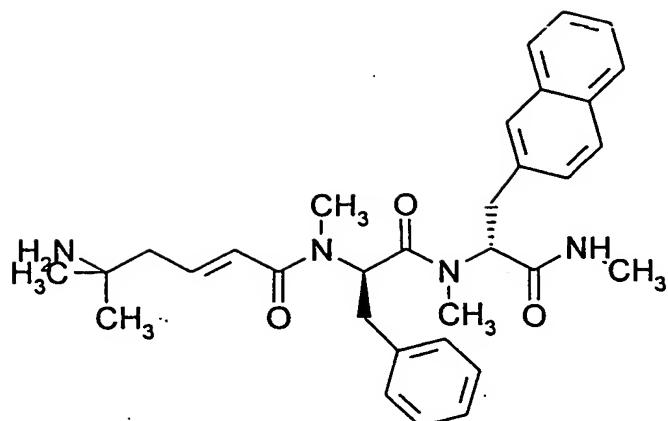
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[((1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



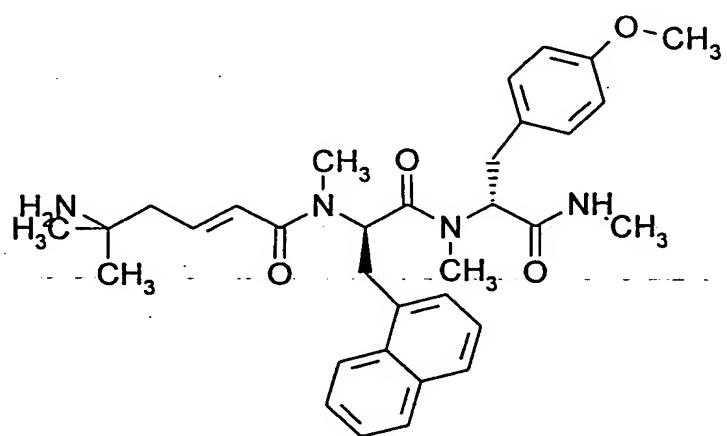
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



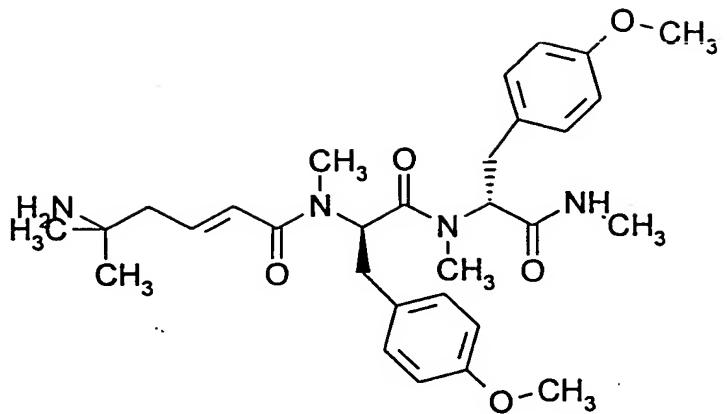
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



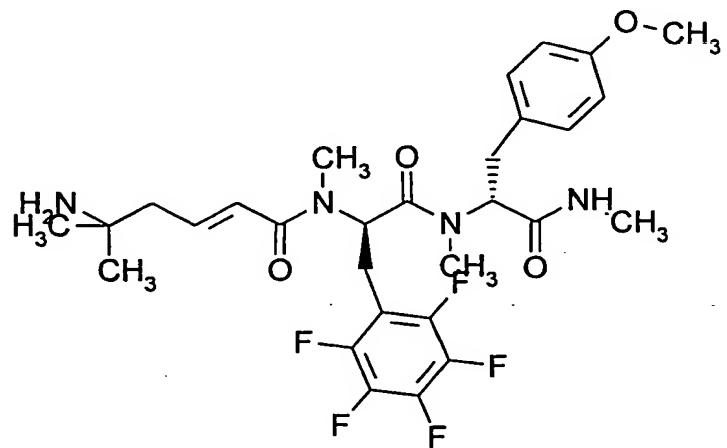
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



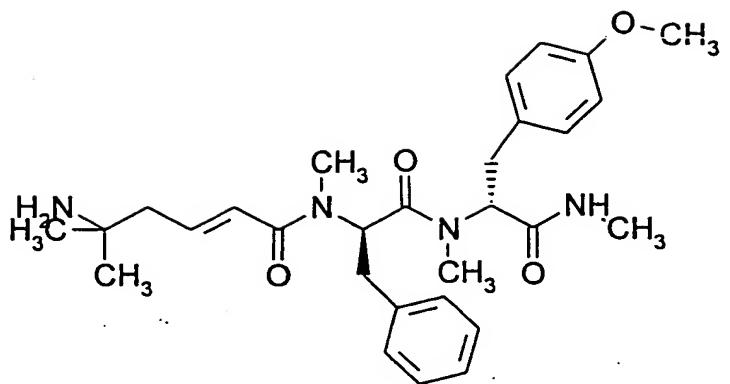
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



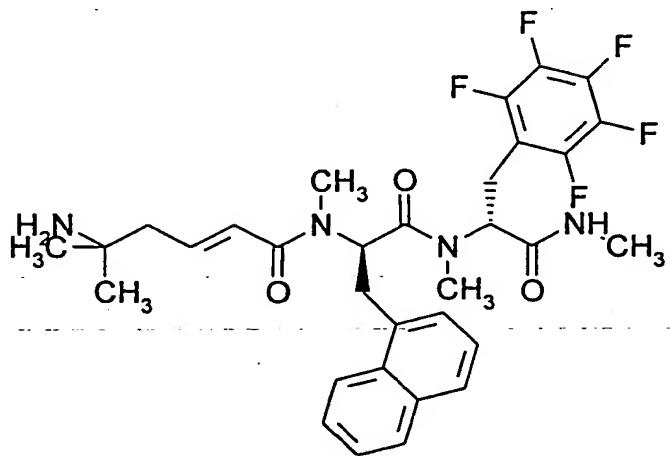
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl}-N-methylcarbamoyl]-2-(2,3,4,5,6-pentafluorophenyl)ethyl}amido):



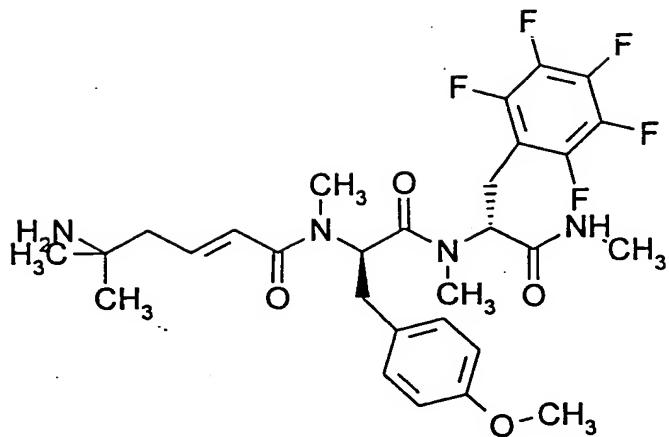
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl}-N-methylcarbamoyl]-2-phenylethyl}amido):



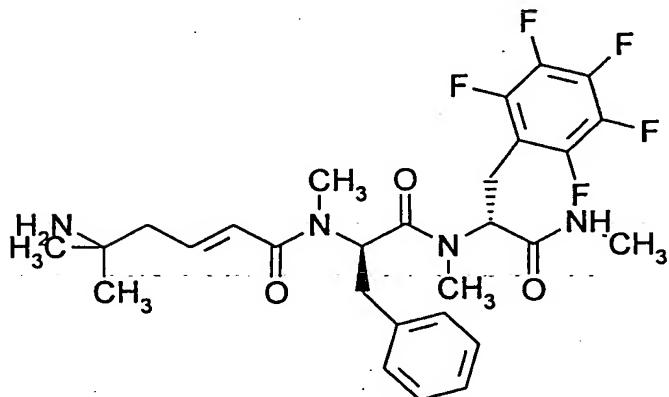
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[((1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



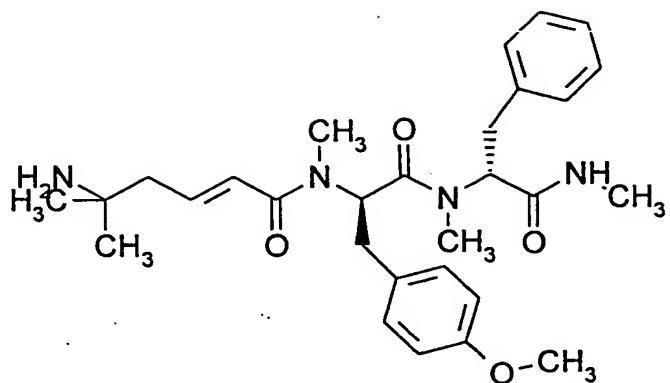
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[((1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



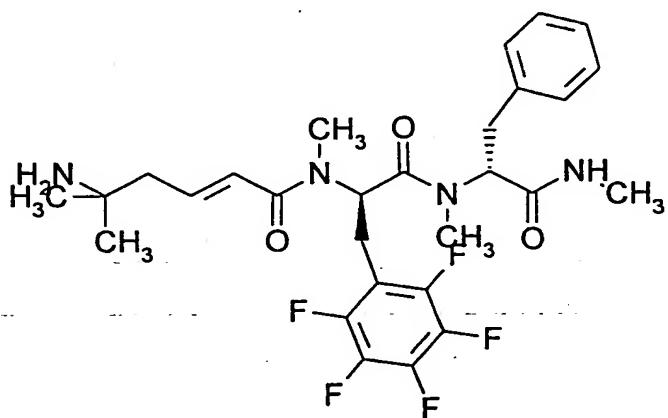
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-phenylethyl)amide:



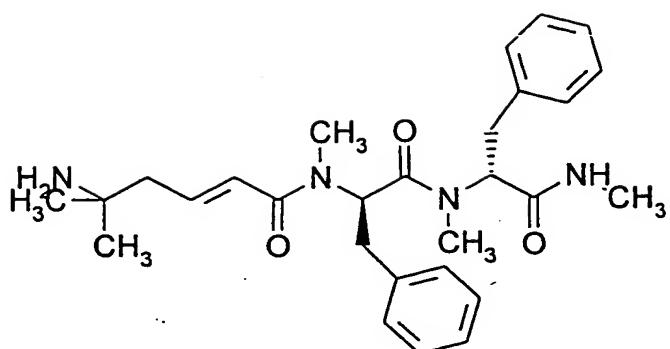
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[((1R)-2-phenyl-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide:

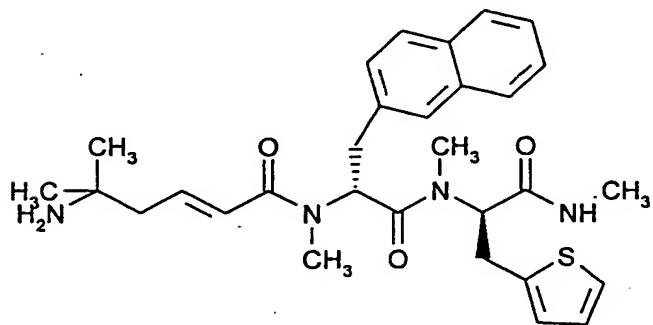


(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[((1R)-2-phenyl-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-phenylethyl)amide:

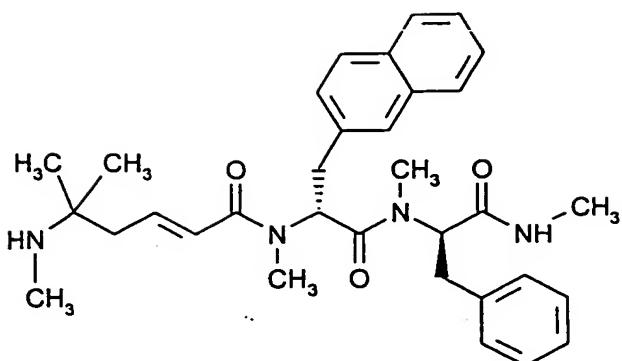


(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide

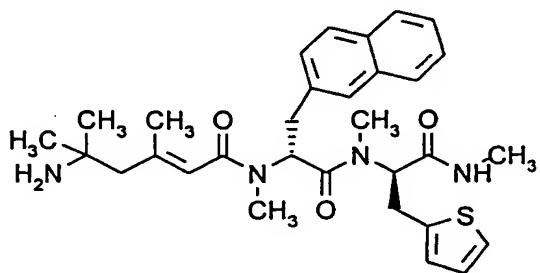
s (2-naphthyl)ethyl)amide



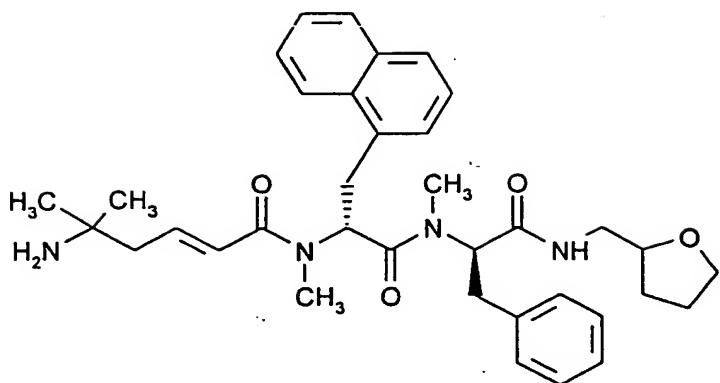
(2E)-5-Methyl-5-methylaminohex-2-enoic acid
N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenyl
ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide



5 (2E)-5-Amino-3,5-dimethylhex-2-enoic acid
 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) amide.

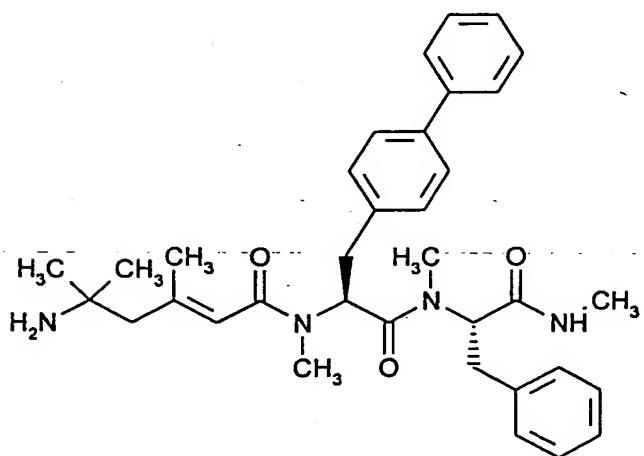


10 (2E)-5-Amino-5-methylhex-2-enoic acid
 N-methyl-N-((1R)-1-(N-methyl-N-(2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl) amide



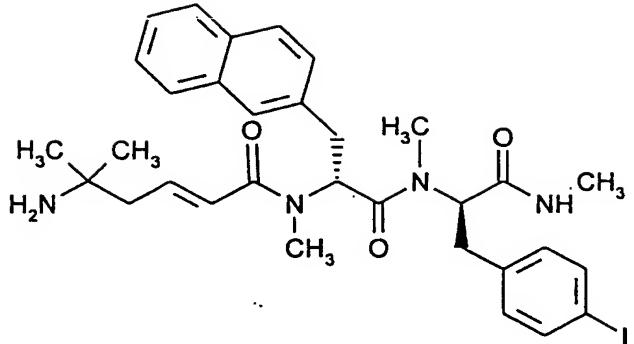
5-Amino-3,5-dimethylhex-2-enoic acid

5 N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide.



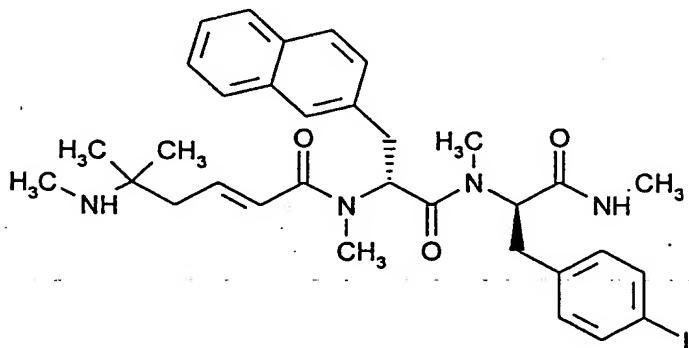
(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

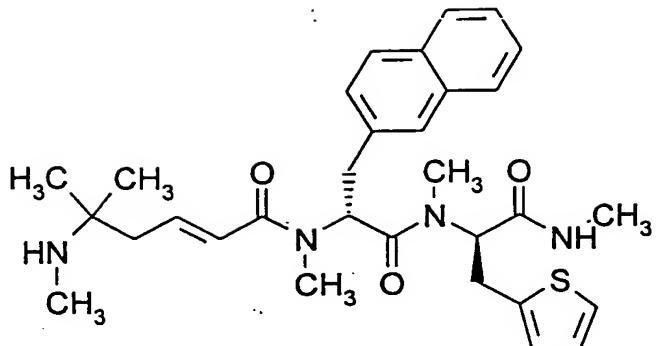


(2E)-5-Methyl-5-methylaminohex-2-enoic acid

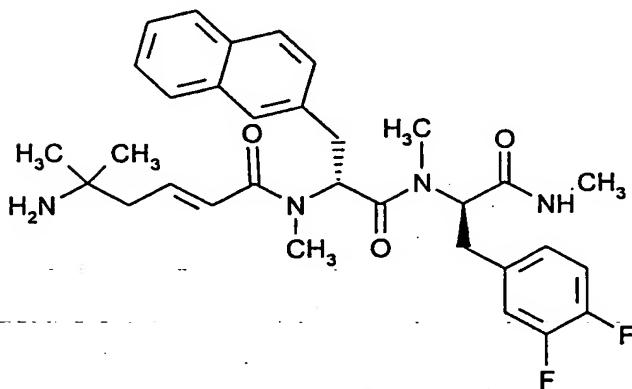
N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



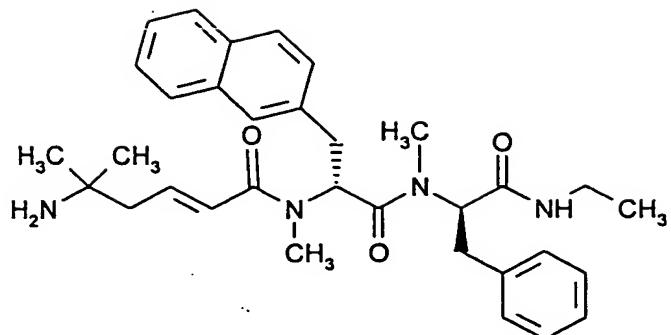
10 (2E)-5-Methyl-5-amino-5-methylhex-2-enoic acid-N-methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(methylcarbamoyl)-2-(thien-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
2-(3,4-difluorophenyl)-1-methylcarbamoylethyl)methylcar-
5 bamoyl)-2-(2-naphthyl)ethyl)methylamide

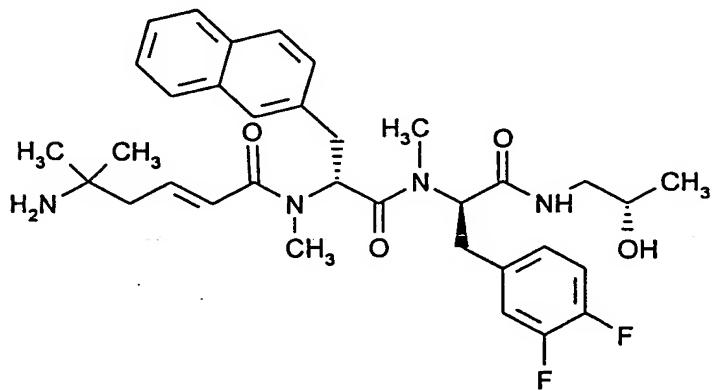


5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
10 2-phenyl-1-ethylcarbamoylethyl)methylcar-
bamoyl)-2-(2-naphthyl)ethyl)methylamide



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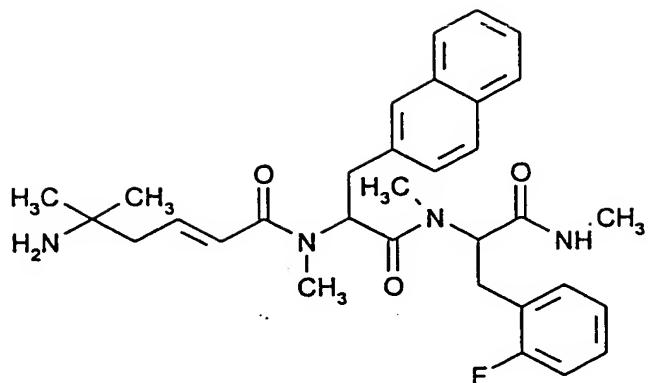
5 5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(3,4-difluorophenyl)ethyl)methylcarbamoyl)-2-(naphthyl)ethyl)methylamide.



10

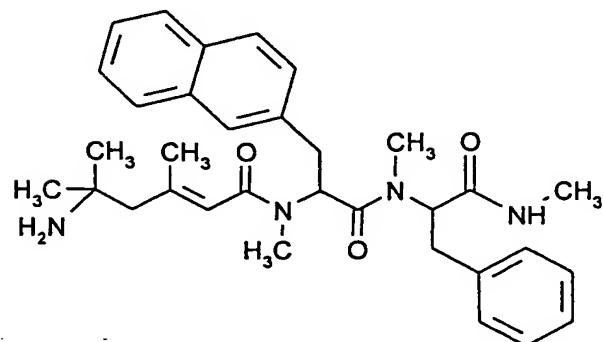
5-Amino-5-methyl-hex-2-enoic acid
(1-{{[2-(2-fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl}-2-(2-naphthyl)ethyl)methylamide.

15

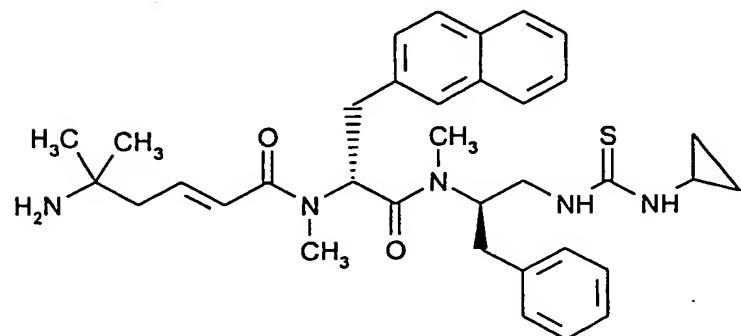


(2Z)-5-Amino-3,5-dimethylhex-2-enoic acid

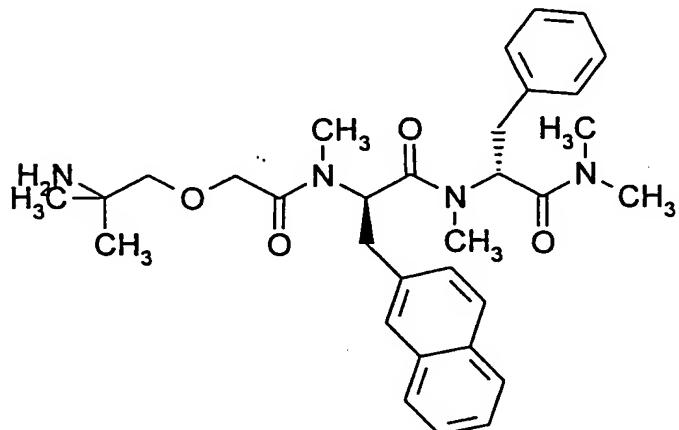
N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



(2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-N-
10 ((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-3-(2-
naphthyl)propionamide



(2R)-2-(N-[{2-Amino-2-methylpropoxy}acetyl]-N-methylamino)-N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide:



5

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide, and its acetate salt;

(2E)-5-Amino-5-methylhex-2-enoic acid

- 10 N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;
- (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-2-(3,4-difluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;
- 15 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;
- (2E) 4-(1-Aminocyclobutyl)-but-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide;
- 20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;
- 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

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(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

5 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

10 3-(1-Aminomethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

15 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzyloxy)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

30 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

5 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;

10 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

20 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

2-naphthyl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

30 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

10 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

15 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

20 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

25 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

5 2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

10 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;

15 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-

25 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

30 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

5 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

10 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

25 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-

30 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)-propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-naphthyl)-ethyl)amide;

5 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

10 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

15 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)-benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)-benzamide;

30 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-

5 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;

10 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(biphen-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-

20 yl)propionamide; or

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide.

25 It is believed that compounds of formula I exhibit an improved resistance to proteolytic degradation by enzymes because they are non-natural, in particular because the natural amide bonds are replaced by non-natural amide bond mimetics. The increased resistance to proteolytic degradation combined with the reduced size of the compounds of the invention in comparison with known hormone

30 releasing peptides is expected to improve their bioavailability compared to that of the peptides suggested in the prior literature.

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

- 5 The C₁₋₆-alkyl groups specified above are intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration, Examples of linear alkyl groups are methyl, ethyl, propyl, butyl, pentyl and hexyl. Examples of branched alkyl groups are isopropyl, sec-butyl, tert-butyl, isopentyl, and isohexyl. Examples of cyclic alkyl are cyclopropyl, cyclobutyl, cyclopentyl and 10 cyclohexyl.

Especially preferred C₁₋₆-alkyl groups are the C₁₋₃-alkyl groups. Preferred C₁₋₃-alkyl groups are methyl, ethyl, isopropyl and cyclopropyl.

- 15 The C₁₋₆-alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, 20 cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

Especially preferred C₁₋₆-alkoxy groups are the C₁₋₃-alkoxy groups. Preferred C₁₋₃-alkoxy groups are methoxy, ethoxy, isopropoxy and cyclopropoxy.

- 25 In the present context, the term C₁₋₆-alkoxycarbonyl is intended to include the above defined C₁₋₆-alkoxy groups attached to a carbonyl moiety.

In the present context, the term C₁₋₆-alkoxycarbonyloxy is intended to include the above defined C₁₋₆-alkoxy groups attached to a carboxyloxy moiety.

30

In the present context, the term "aryl" is intended to include aromatic rings, such as carboxyclic and heterocyclic aromatic rings selected from the group consisting of

phenyl, naphthyl, pyridyl, tetrazolyl, thiazolyl, imidazolyl, indolyl, quinolinyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thienyl, furanyl or oxadiazolyl optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy. Aryl is preferably phenyl, thienyl, imidazolyl, pyridyl, indolyl, oxadiazole or naphthyl

5 optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy.

The term "halogen" includes Cl, F, Br and I.

The compounds of the present invention may have one or more asymmetric

10 centres and it is intended that stereoisomers, as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

Pharmaceutically acceptable acid addition salts of compounds of formula I include

15 those prepared by allowing the compound to react with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, acetic, phosphoric, lactic, maleic, phthalic, citric, glutaric, gluconic, methanesulfonic, salicylic, succinic, tartaric, toluenesulfonic, trifluoroacetic, sulfamic or fumaric acid.

20 In another aspect, the present invention relates to a pharmaceutical composition comprising, as an active ingredient, a compound of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

25 Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington's Pharmaceutical Sciences, 1985. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

30

The pharmaceutical carrier or diluent employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose,

cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water.

5 Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier is used for oral administration, the preparation may be tabletted,
 10 placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

15

A typical tablet which may be prepared by conventional tabletting techniques may contain:

20 Core:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg

25 Magnesium stearate

Coating:

HPMC approx.	9 mg
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*Mywacett 9-40 T approx.	0.9 mg
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30

*Acylated monoglyceride used as plasticizer for film coating.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, 5 e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising 50-200 mg of active ingredient together with a pharmaceutically 10 acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is suitably 0.1-500 mg/day, e.g. from about 5 to about 50 mg, such as about 10 mg per dose, when administered to patients, e.g. humans, as a drug.

15 The compounds of the invention possess interesting pharmacological properties, and it has been demonstrated that compounds of the general formula I possess the ability to release endogenous growth hormone *in vivo*. The compounds may therefore be used in the treatment of conditions which require increased plasma 20 growth hormone levels such as in growth hormone deficient humans or in elderly patients or livestock.

Thus, in a particular aspect, the present invention relates to a pharmaceutical composition for stimulating the release of growth hormone from the pituitary, the 25 composition comprising, as an active ingredient, a compound of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of stimulating the 30 release of growth hormone from the pituitary, the method comprising administering to a subject in need thereof an effective amount of a compound of the general formula I or a pharmaceutically acceptable salt thereof.

In a still further aspect, the present invention relates to the use of a compound of the general formula I or a pharmaceutically acceptable salt thereof for the preparation of a medicament for stimulating the release of growth hormone from the pituitary.

To those skilled in the art, it is well known that the current and potential uses of growth hormone in humans are varied and multitudinous. Thus, compounds of formula I can be administered for purposes stimulating release of growth hormone

from the pituitary and would then have similar effects or uses as growth hormone itself. The uses of growth hormone may be summarized as follows: stimulation of growth hormone release in the elderly; prevention of catabolic side effects of glucocorticoids, prevention and treatment of osteoporosis, stimulation of the immune system, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting from growth retardation, treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome;

accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients, treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation, treatment of pulmonary dysfunction and ventilator dependency, attenuation of protein catabolic responses after major surgery, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis, adjuvant treatment for ovulation induction; to stimulate thymic development and prevent the age-related decline of thymic function, treatment of immunosuppressed patients, improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly, stimulation of osteoblasts, bone

remodelling and cartilage growth, stimulation of the immune system in companion animals and treatment of disorder of aging in companion animals, growth promoter in livestock and stimulation of wool growth in sheep.

- 5 For the above indications the dosage will vary depending on the compound of formula I employed, on the mode of administration and on the therapy desired. However, generally dosage levels between 0.0001 and 100 mg/kg body weight daily are administered to patients and animals to obtain effective release of endogenous growth hormone. Usually, dosage forms suitable for oral, nasal,
- 10 pulmonary or transdermal administration comprise from about 0.0001 mg to about 100 mg, preferably from about 0.001 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form or, where appropriate, as a alkali metal or alkaline earth metal or lower alkylammonium salt. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

Optional, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more compounds exhibiting a different activity, e.g., an antibiotic or other pharmacologically active material.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral, the oral route being preferred.

Apart from the pharmaceutical use of the compounds of formula I, they may be useful in vitro tools for investigating the regulation of growth hormone release.

Compounds of formula I may also be useful in vivo tools for evaluating the growth hormone releasing capability of the pituitary. For example, serum samples taken before and after administration of these compounds to humans can be assayed for

growth hormone. Comparison of the growth hormone in each serum sample would directly determine the ability of the patients pituitary to release growth hormone.

Compounds of formula I may be administered to commercially important animals to
5 increase their rate and extent of growth, and to increase milk production.

A further use of growth hormone secretagogue compounds of formula I is in combination with other secretagogues such as GHRP (2 or 6), GHRH and its analogues, growth hormone and its analogues or somatomedins including IGF-1
10 and IGF-2.

Pharmacological Methods

Compounds of formula I may be evaluated in vitro for their efficacy and potency to
15 release growth hormone in rat pituitary primary cultures.

The isolation of rat pituitary cells is a modification of O. Sartor et al., Endocrinology 116, 1985, pp. 952-957. Male albino Sprague-Dawley rats (250 +/- 25 grams) were purchased from Møllegaard, Lille Skensved, Denmark. The rats were housed in
20 group cages (four animals/cage) and placed in rooms with 12 hour light cycle. The room temperature varied from 19-24°C and the humidity from 30 - 60%.

The rats were decapitated and the pituitaries dissected. The neurointermediate lobes were removed and the remaining tissue was immediately placed in icecold
25 isolation buffer (Gey's medium (Gibco 041-04030) supplemented with 0.25% D-glucose, 2% non-essential amino acids (Gibco 043-01140) and 1% bovine serum albumine (BSA) (Sigma A-4503)). The tissue was cut into small pieces and transferred to isolation buffer supplemented with 3.8 mg/ml of trypsin (Worthington #3707 TRL-3) and 330 mg/ml of DNase (Sigma D-4527). This mixture was
30 incubated at 70 rotations/min for 35 min at 37°C in a 95/5% atmosphere of O₂/CO₂. The tissue was then washed three times in the above buffer. Using a standard pasteur pipet, the tissue was then aspirated into single cells. After dispersion, cells

were filtered through a nylon filter (160 mm) to remove undigested tissue. The cell suspension was washed 3 times with isolation buffer supplemented with trypsin inhibitor (0.75 mg/ml, Worthington #2829) and finally resuspended in culture medium; DMEM (Gibco 041-01965) supplemented with 25 mM HEPES (Sigma H-3375), 4 mM glutamine (Gibco 043-05030H), 0.075% sodium bicarbonate (Sigma S-8875), 0.1% non-essential amino acid, 2.5% fetal calf serum (FCS, Gibco 011-06290), 3% horse serum (Gibco 034-06050), 10% fresh rat serum, 1 nM T₃ (Sigma T-2752) and 40 mg/L dexamethasone (Sigma D-4902) pH 7.3, to a density of 2 x 10⁵ cells/ml. The cells were seeded into microtiter plates (Nunc, Denmark), 200 - 10 ml/well, and cultured for 3 days at 37°C and 8% CO₂.

Compound testing

After culturing, the cells were washed twice with stimulation buffer (Hanks Balanced Salt Solution (Gibco 041-04020) supplemented with 1% BSA (Sigma A-4503), 0.25% D-glucose (Sigma G-5250) and 25 mM HEPES (Sigma H-3375) pH 7.3) and preincubated for 1 hour at 37°C. The buffer was exchanged with 90 ml stimulation buffer (37°C). Ten ml test compound solution was added and the plates were incubated for 15 min at 37°C and 5% CO₂. The medium was decanted and 20 analyzed for GH content in an rGH SPA test system.

All compounds were tested in doses ranging from 10 pM to 100 mM. A dose-response relation was constructed using the Hill equation (Fig P, Biosoft). The efficacy (maximal GH released, E_{max}) was expressed in % of the E_{max} of GHRP-6. 25 The potency (EC₅₀) was determined as the concentration inducing half maximal stimulation of the GH release.

30 Compounds of formula I may be evaluated for their metabolic stability.

Compounds were dissolved at a concentration of 1 mg/ml in water. 25 ml of this solution is added to 175 ml of the respective enzyme-solution (resulting in an enzyme:substrate ratio (w/w) of approximately 1:5). The solution is left at 37°C overnight. 10 ml of the various degradation solutions is analyzed against a

5 corresponding zero-sample using flow injection electrospray mass spectrometry (ESMS) with selected ion monitoring of the molecular ion. If the signal has decreased more than 20% compared to the zero-sample, the remainder of the solution is analyzed by HPLC and mass spectrometry in order to identify the extent and site(s) of degradation precisely.

10

Several standard peptides (ACTH 4-10, Angiotensin 1-14 and Glucagon) have been included in the stability tests in order to verify the ability of the various solutions to degrade peptides.

15 Standard peptides (angiotensin 1-14, ACTH 4-10 and glucagon) were purchased from Sigma, MO, USA)

Enzymes (trypsin, chymotrypsin, elastase aminopeptidase M and carboxypeptidase Y and B) were all purchased from Boehringer Mannheim GmbH (Mannheim, 20 Germany)

Pancreatic enzyme mix: trypsin, chymotrypsin and elastase in 100 mM ammoniumbicarbonate pH 8.0 (all concentrations 0.025 mg/ml).

25 Carboxypeptidase mix: carboxypeptidase Y and B in 50 mM ammoniumacetate pH 4.5 (all concentrations 0.025 mg/ml).

Aminopeptidase M solution: aminopeptidase M (0.025 mg/ml) in 100 mM ammoniumbicarbonate pH 8.0

30

Mass spectrometric analysis was performed using two different mass spectrometers. A Sciex API III triple quadrupole LC-MS instrument (Sciex

instruments, Thornhill, Ontario) equipped with an electrospray ion-source and a Bio-Ion 20 time-of-flight Plasma Desorption instrument (Bio-Ion Nordic AB, Uppsala, Sweden).

- 5 Quantification of the compounds (before and after degradation) was done on the API III instrument using single ion monitoring of the molecular ion in question with flow injection of the analyte. The liquid flow (MeOH:water 1:1) of 100 ml/min was controlled by an ABI 140B HPLC unit (Perkin-Elmer Applied Biosystems Divisions, Foster City, CA). The instrument parameters were set to standard operation
- 10 conditions, and SIM monitoring was performed using the most intense molecular ion (in most cases this corresponded to the doubly charged molecular ion).

Identification of degradation products furthermore involved the use of plasma desorption mass spectrometry (PDMS) with sample application on nitrocellulose
15 coated targets and standard instrumental settings. The accuracy of the hereby determined masses is generally better than 0.1%.

Separation and isolation of degradation products was done using a HY-TACH C-18 reverse phase 4.6x105 mm HPLC column (Hewlett-Packard Company, Palo Alto,
20 CA) with a standard acetonitrile: TFA separation gradient. The HPLC system used was HP1090M (Hewlett-Packard Company, Palo Alto, CA).

Peptide derivative	MW/SIM ion (amu)	Carbox y-peptidase mix	Pan. enzyme mix
Standards			
ACTH 4-10	1124.5/5 62.8	+	-
Glucagon	3483/871 .8	-	-
Insulin (B23-29)	859.1/43 0.6		
Angiotensin 1-14	1760.1/8 81.0	-	-
GHRP-2	817.4/40 9.6	-	-
GHRP-6	872.6/43 7.4	-	-

+: Stable (less than 20% decrease in SIM signal after 24 h in degradation solution)

5 -: Unstable (more than 20% decrease in SIM signal after 24 h in degradation solution)

Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES:

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (*d*) are given in parts per million (ppm) and only selected peaks are given. mp is

10 melting point and is given in °C. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

15

Abbreviations:

TLC: thin layer chromatography
DMSO: dimethylsulfoxide
CDCl₃: deuterated chloroform
20 DMF: N,N-dimethylformamide
min: minutes
h: hours

HPLC-Analysis:

25

Method B1.

The RP-HPLC analysis was performed using UV detection at 214nm and a Vydac 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1ml/minute. Two solvent systems were used:
30 Solvent system I: 0.1% Trifluoroacetic acid in acetonitrile. Solvent system II: 0.1% Trifluoroacetic acid in water.

The column was equilibrated with a mixture composed of 5% of solvent system I and 95% of solvent system II. After injection of the sample a gradient of 5% to 60% of solvent system I in solvent system II was run over 50 minutes. The gradient was then extended to 100% of solvent system I over 15 minutes followed by isocratic elution with 100% of this system for 5 minutes.

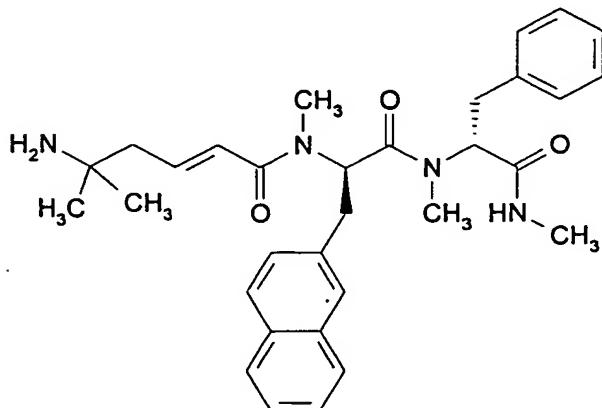
Method A1.

The RP-analysis was performed using UV detections at 214, 254, 276, and 301 nm on a Vydac 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1 mL/min at 42°C. The column was equilibrated with 5% acetonitrile in a buffer consisting of 0.1 M ammonium sulfate, which was adjusted to pH 2.5 with 4M sulfuric acid. after injection the sample was eluted by a gradient of 5% to 60% acetonitrile in the same buffer during 50 min.

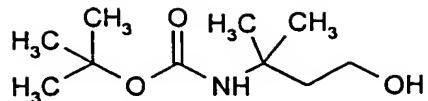
15

Example 1:

(2E) 5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide
20 hydrochloride:



3-Hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester:

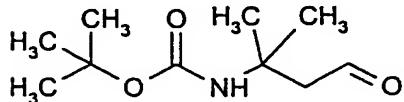


Step A: At 0 °C, ethyl chloroformate (1.10 mL, 11.5 mmol) was given dropwise to a solution of 3-tert-butoxycarbonylamino-3-methylbutanoic acid (2.50 g, 11.5 mmol) and triethylamine (1.92 mL, 13.8 mmol) in tetrahydrofuran (10 mL). The solution was stirred for 40 min at 0 °C. The formed precipitate was filtered off and washed with tetrahydrofuran (20 mL). The liquid was immediately cooled to 0 °C. A 2M solution of lithium boronhydride in tetrahydrofuran (14.4 mL, 28.8 mmol) was added dropwise. The solution was stirred at 0 °C for 2 h, and then warmed to room temperature over a period of 4 h. It was cooled to 0 °C. Methanol (5 mL) was added carefully. 1N Hydrochloric acid (100 mL) was added. The solution was extracted with ethyl acetate (2 x 100 mL, 3 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was chromatographed on silica (110 g) with ethyl acetate/heptane 1:2 to give 1.84 g of 3-hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): δ 1.33 (s, 6 H); 1.44 (s, 9 H); 1.88 (t, 2 H); 1.94 (br, 1 H); 3.75 (q, 2 H); 4.98 (br, 1 H).

20

3-(tert-Butoxycarbonylamino)-3-methylbutanal:



25

Step B: DMSO (1.22 mL, 17.2 mmol) was added to a solution of oxalyl chloride (1.1 mL, 12.9 mmol) at -78 °C in dichloromethane (15 mL). The mixture was stirred for 15 min at -78 °C. A solution of 3-hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester (1.75 g, 8.6 mmol) in dichloromethane (10 mL) was added dropwise over a

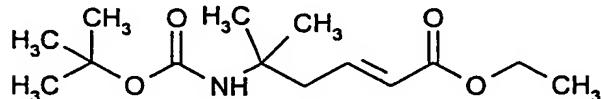
period of 15 min. The solution was stirred at -78 °C for another 15 min.

Triethylamine (6.0 mL, 43 mmol) was added. The solution was stirred at -78 °C for 5 min and then warmed to room temperature. The solution was diluted with dichloromethane (100 mL) and extracted with 1N hydrochloric acid (100 mL). The

5 aqueous phase was extracted with dichloromethane (50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica (140 g) with ethyl acetate/heptane (1:3) to give 1.10 g of 3-(tert-butoxycarbonylamino)-3-methylbutanal.
10

MHz-¹H-NMR (CDCl₃): d 1.39 (s, 6 H); 1.45 (s, 9 H); 2.85 (d, 2 H); 4.73 (br. 1 H); 9.80 (t, 1 H).

15 Ethyl (2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoate:

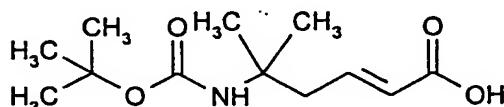


Step C: Triethylphoshonoacetate (1.96 mL, 9.8 mmol) was dissolved in

20 tetrahydrofuran (30 mL). Potassium tert-butoxide (1.10 g, 9.8 mmol) was added. The solution was stirred for 40 min at room temperature. A solution of 3-(tert-butoxycarbonylamino)-3-methylbutanal (1.10 g, 5.5 mmol) in Tetrahydrofuran (6 mL) was added. The solution was stirred at room temperature. for 75 min. It was diluted with ethyl acetate (100 mL) and 1N hydrochloric acid (100 mL). The phases
25 were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution (60 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica (90 g) with ethyl acetate/heptane (1:4) to give 1.27 g of ethyl (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoate.
30

¹H-NMR (CDCl₃): d 1.30 (s, 6 H); 1.30 (t, 3 H); 1.46 (s, 9 H); 2.62 (d, 2 H); 4.27 (q, 2 H); 4.42 (br, 1 H); 5.88 (d, 1 H); 6.94 (td, 1 H).

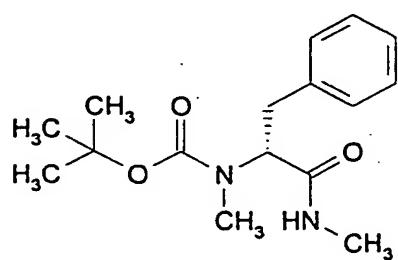
5 (2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid:



Step D: Ethyl (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoate (1.233 g, 4.54 mmol) was dissolved in dioxane (20 mL). Lithium hydroxide (0.120 g, 5.00 mmol) was added as a solid. Water (10 mL) was added, until a clear solution was reached. The solution was stirred 16 h at room temperature. The solution was diluted with water (70 mL) and was extracted with tert-butyl methyl ether (2 x 100 mL). The aqueous phase was acidified with 1N sodium hydrogensulfate solution (pH = 1) and was extracted with tert-butylmethylether (3 x 70 mL). The organic phases were combined and dried over magnesium sulfate. The solvent was removed in vacuo to give 1.05 g of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid. The crude product was used for further syntheses.

¹H-NMR (DMSO d₆): d 1.15 (s, 6 H); 1.35 (s, 9 H); 2.53 (d, 2 H); 5.75 (d, 1 H); 6.57 (br, 1 H); 6.75 (td, 1 H); 12.15 (s, 1 H).

N-Methyl-N-((R)-1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester:

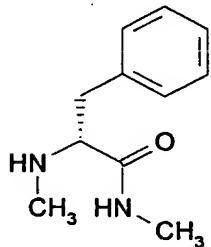


25 Step E: N-Tert-butoxycarbonyl-N-methyl-D-phenylalanine (1.22 g, 4.4 mmol), 1-hydroxybenzotriazole hydrate(0.59 g, 4.4 mmol) and 1-ethyl-3-(3-dimethyl-

aminopropyl)carbodiimid hydrochloride (0.88 g, 4.6 mmol) were dissolved in N,N-dimethylformamide (25 mL) and stirred for 30 min. Methylamine (0.51 g of a 40% solution in methanol, 6.6 mmol) was added and the mixture was stirred overnight. Methylene chloride (80 mL) and water (100 mL) were added and the phases were separated. The organic phase was washed with sodium hydroxide (20 mL, 1N), sodium hydrogensulfate (50 mL, 10 %) and water (50 mL). The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to afford 1.39 g of N-methyl-N-((R)1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester.

10 $^1\text{H-NMR}$ (CDCl_3): d 1.25, 1.35 (two s (br), 9H); 2.73-2.94 (m, 7H); 3.30-3.50 (m, 1H); 4.68, 4.90 (two m, 1H); 5.90, 6.12 (two s (br); 1H); 7.12-7.25 (m, 5H).

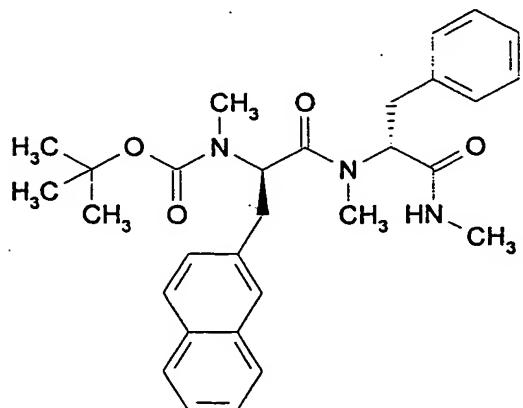
(R)-N-Methyl-2-methylamino-3-phenylpropionamide:



15 Step F: N-Methyl-N-((R)1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester (1.39 g, 7.23mmol) was dissolved in a mixture of trifluoroacetic acid (5 mL) and methylene chloride (10 mL) and stirred for 45 min. The volatiles were removed in vacuo and the residue was stirred with a mixture of ethyl acetate (100 mL) and water (100 mL). Sodium hydrogen carbonate (50 mL, saturated) was added and the phases were separated. The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to afford 330 mg of (R)-N-methyl-2-methylamino-3-phenylpropionamide.

25 $^1\text{H-NMR}$ (CDCl_3): d 2.1 (s(br), 3H); 2.32 (s, 3H); 2.77 (dd, 1H); 2.81 (two s, 3H); 3.21 (dd, 1H); 3.32 (dd, 1H); 7.12 (s(br), 1H); 7.20-7.34 (m, 5H).

N-Methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl}carbamic acid tert-butyl ester:



5 **Step G:** (R)-Tert-butoxycarbonyl-N-methylamino-3-(2-naphthyl)propionic acid (548 mg, 1.66 mmol) was dissolved in methylene chloride (5 mL); 1-hydroxy-7-azabenzotriazole (227 mg, 1.66 mmol) was added along with N,N-dimethylformamide (2 mL). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (351 mg, 1.83 mmol) was added and the solution was stirred for 15 min.

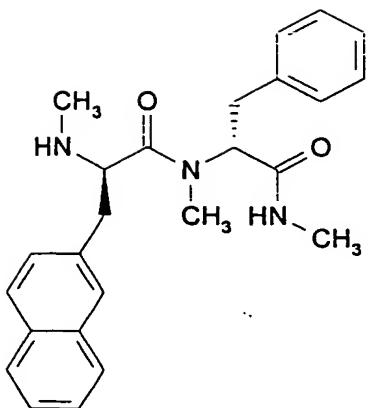
10 (R)-N-Methyl-2-methylamino-3-phenylpropionamide (320 mg, 1.66 mmol) dissolved in methylene chloride (4 mL) and diisopropylethylamine (0.28 mL, 1.66 mmol) were added and the mixture was stirred overnight. Methylene chloride (50 mL) was added and the organic phase was washed with water (100 mL), sodium hydrogensulfate (50 mL, 5%) and sodium hydrogen carbonate (50 mL, saturated).

15 The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo. The residue was chromatographed (silica, 2 x 45 cm) using ethylacetate/methylene chloride (1:1) to afford 604 mg of N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)-ethyl)carbamic acid tert-butyl ester.

20

¹H-NMR (CDCl_3): δ 1.05, 1.31, 1.56 (three s, 9H); 2.28-3.37 (several m, 13 H); 5.04, 5.17, 5.29, 5.48 (four dd, 2H); 7.05-7.79 (m, 12 H).

(2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide:

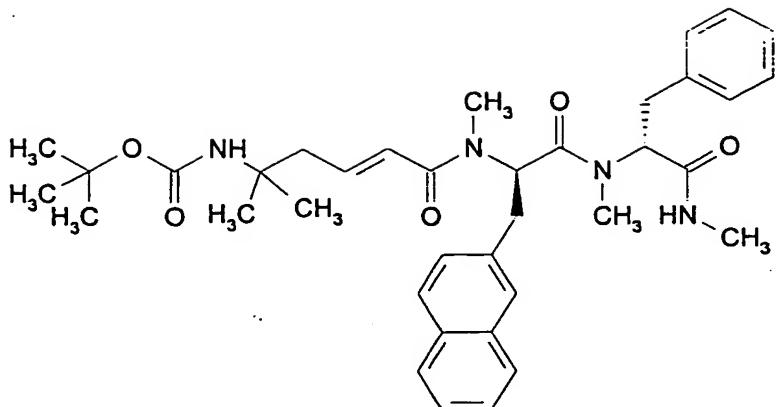


Step H: N-Methyl-N-{(1R)-1-(N-methyl-N-{(1R)-1-(methylcarbamoyl)-2-phenylethyl}carbamoyl)-2-(2-naphthyl)ethyl}carbamic acid tert-butyl ester (600 mg, 1.19 mmol) was stirred in trifluoroacetic acid/methylene chloride (1:1, 5 mL) for 10 min and the volatiles were removed in vacuo. The residue was stripped with diethylether (2 x 5 mL) and dissolved in methanol (2 mL) and mixed with sodium hydrogen carbonate (10 mL) and ethylacetate (15 mL). The organic phase was separated and dried (magnesium sulfate) to afford 420 mg of (2R)-N-methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide.

¹H-NMR (CDCl₃): (selected values) d 1.69 (s, 3H); 2.08 (d, 3H); 2.54 (s, 3H); 2.76 (dd, 1H); 2.92 (dd, 1H), 3.12 (dd, 1H), 3.31 (dd, 1H); 3.72 (dd, 1H), 4.95 (q (br), 1H); 5.50 (dd, 1H).

15

((3E)-1,1-Dimethyl-4-(N-methyl-N-{(1R)-1-(N-methyl-N-{(1R)-1-(methylcarbamoyl)-2-phenylethyl}carbamoyl)-2-(2-naphthyl)ethyl}carbamoyl)but-3-enyl)carbamic acid tert-butyl ester:



Step I: (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (200 mg, 0.82 mmol), 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol) and 1-ethyl-3-(3-s dimethylaminopropyl)-carbodiimide hydrochloride (173 mg, 0.90 mmol) were dissolved in a mixture of methylene chloride (10 mL) and N,N-dimethylformamide (1 mL) and stirred for 15 min. N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (332 mg, 0.82 mol) dissolved in methylene chloride (5 mL) and diisopropylethylamine (0.14 mL) were added and 10 the mixture was stirred overnight under nitrogen atmosphere. The mixture was diluted with methylene chloride (50 mL), washed with water (50 mL), sodium hydrogen carbonate (30 mL, saturated), and sodium hydrogensulfate (30 mL, 5%). The phases were separated and the organic phase was dried with magnesium sulfate and evaporated in vacuo. The residue was chromatographed (silica, 2 x 40 cm) to afford 450 mg of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)-carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): (selected values) d 1.20, 1.22, 1.24, 1.30, 1.41, 1.55 (six s, 15 H), 20 4.30, 4.40 (two s (br), 1H); 5.08, 5.18, 5.32, 5.60, 5.87 (five dd, 2H); 6.05 (dd, 1H); 6.75 (m, 1H).

Step J: ((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)but-3-enyl)carbamic acid 25 tert-butyl ester (403 mg, 0.63 mmol) was stirred in a mixture of trifluoroacetic acid

(4mL) and methylene chloride (4 mL) for 10 min. The volatiles were removed in vacuo and the crude product was chromatographed on silica (400g) using a mixture of methylene chloride, ethanol and ammonia (25% in water) (80/18/2) as eluent. The isolated product was dissolved in 3M hydrochloric acid in ethyl acetate and 5 evaporated, then redissolved in methylene chloride and evaporated twice to afford 140 mg of the title compound.

¹H-NMR (CDCl₃): δ 1.05, 1.10, 1.15, 1.16 (four s, 6H); 2.07 (s (br); 3H); 5.12, 5.32, 5.40, 5.60, 5.91 (five dd, 2H); 6.05, 6.14 (two d, 1H); 6.80 (m, 1H)

10

HPLC: R_t = 29.02 min (Method A1)

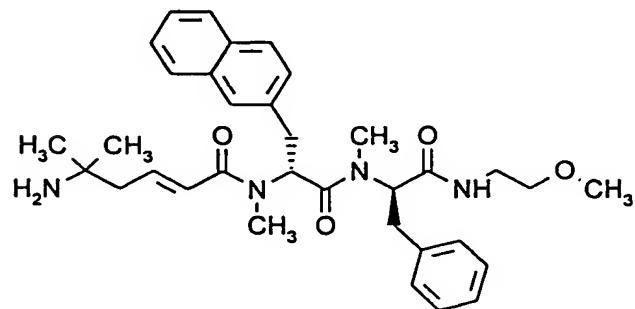
ESMS: m/z = 529 (100%)(M+H)⁺

15

Example 2:

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((2-methoxyethyl)-carbamoyl)-2-phenylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

20



This compound was prepared analogously to example 1. 2-methoxyethylamine was 25 substituted for methylamine in step E.

¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) δ 1.05; 1.10 (two d, 6H),

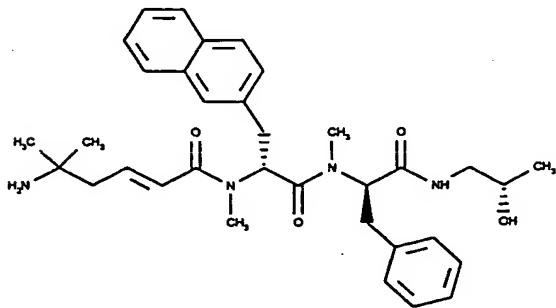
3.34 (s, 3H), 6.02 (d, 1H)

HPLC: $R_t = 30.47$ min (Method A1)

5 PDMS: $m/z = 573.3$ (100%) ($M+H$)⁺

Example 3:

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-phenylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



15

This compound was prepared analogously to example 1. (S)-2-hydroxypropylamine was substituted for methylamine in step E.

20 $^1\text{H-NMR}$ (CDCl_3) (selected peaks, mixture of rotamers) d 3.90 (m, 1H); 5.55 (dd, 1H); 5.58 (d, 1H)

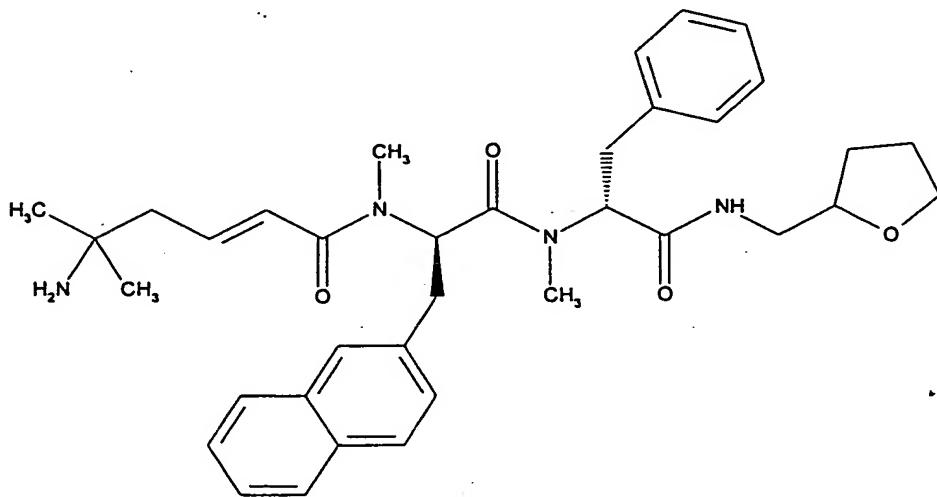
HPLC: $R_t = 29.03$ min (Method A1)

PDMS: $m/z = 573.5$ (100%) ($M+H$)⁺

25

Example 4:

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(methyl-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)-carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)amide:



10 This compound was prepared analogously to example 1. 2-(methylamino)tetrahydrofuran was substituted for methylamine in step E.

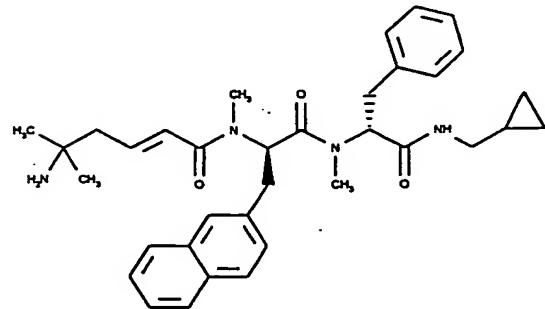
¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) d 1.06, 1.09 (two d, 6H); 2.78 (d, 2H); 5.25-5.62 (m, 2H); 6.05 (m, 1H)

15

HPLC: R_t = 33.65 min (method A1)

Example 5:

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((cyclopropylmethyl)-carbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



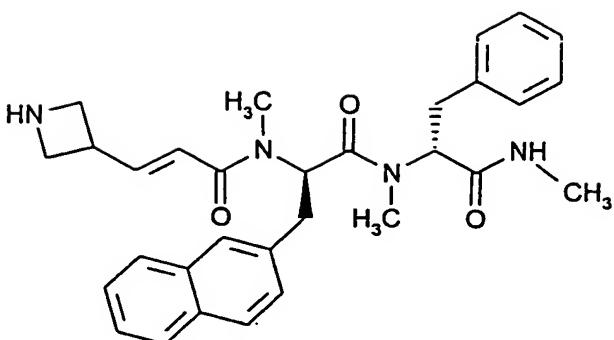
This compound was prepared analogously to example 1. Cyclopropylmethylamine
10 was substituted for methylamine in step E.

¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) δ 0.08-0.20 (m, 2H); 1.05;
1.15 (two s, 6H); 6.02, 6.05 (two d, 1H)

15 HPLC: R_t = 35.7 min (Method A1)

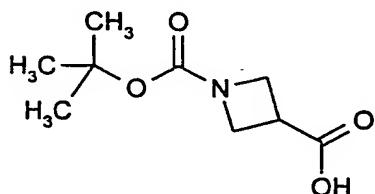
Example 6

20 (2E)-3-(Azetidin-3-yl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)acrylamide:



3-Carboxyazetidine-1-carboxylic acid tert-butyl ester.

5

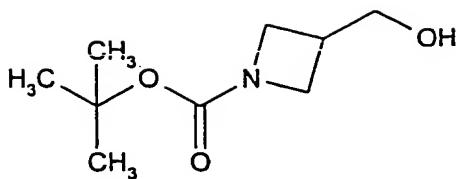


Azetidine-3-carboxylic acid (10.0 g; 98.9 mmol) was dissolved in tetrahydrofuran (120 mL) and water (20 mL). An aqueous solution of sodium hydroxide (10 mL; 1 N) was added. Di-tert butyl dicarbonate (25.9 g; 118.7 mmol) was dissolved in tetrahydrofuran (80 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred for 12 hours at room temperature and evaporated in vacuo. To the residue was added water (100 mL) and an aqueous solution of sodium hydroxide (100 mL; 1N) and the aqueous phase was extracted with diethyl ether (2 x 100 mL). The aqueous phase was acidified with an aqueous solution of sodium hydrogensulfate (1 M) until pH 2. Diethyl ether (200 mL) was added and the organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 20 g of 3-carboxyazetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) d 1.43 (s, 9H); 3.37 (p, 1H); 4.14 (d, 4H); 10.05 (s, 1H).

20

3-Hydroxymethylazetidine-1-carboxylic acid tert-butyl ester.

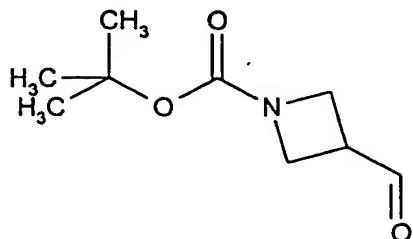


1-Carboxyazetidine-1-carboxylic acid tert-butyl ester (5.0 g; 24.8 mmol) was dissolved in dry tetrahydrofuran. Triethylamine (4.1 mL; 29.8 mmol) was added and the reaction mixture was cooled to 0°C. Ethyl chloroformate (2.4 mL; 24.8 mmol) was added and the reaction mixture was stirred for 40 min at 0°C. The reaction mixture was filtered and the filter cake was washed with dry tetrahydrofuran (30 mL). The combined filtrates were cooled to 0°C and lithium borohydride (2.0 M in tetrahydrofuran; 31 mL; 62.1 mmol) was added dropwise to the reaction mixture and it was then heated to room temperature and stirred for 12 hours. The reaction mixture was cooled to 0°C and methanol (10 mL) was added dropwise. An aqueous solution of sodium hydrogen carbonate (100 mL; 10 %) was added and the reaction mixture was extracted with ethyl acetate (4 x 100 mL). The combined organic phases were washed with a saturated solution of sodium hydrogen carbonate (100 mL), dried (magnesium sulfate) and evaporated in vacuo to afford 3.43 g of 3-hydroxymethylazetidine-1-carboxylic acid tert-butyl ester.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43 (s, 9H); 2.7 (p, 1H); 3.63-3.70 (m, 2H), 3.74 (d, 1H); 3.88 (d, 1H); 3.9-4.0 (m, 2H).

20

3-Formylazetidine-1-carboxylic acid tert-butyl ester.



25

Oxalyl chloride (2.1 mL; 24.0 mmol) was dissolved in methylene chloride (30 mL) and cooled to -78°C. Dimethyl sulfoxide (2.3 mL; 32.0 mmol) was added.

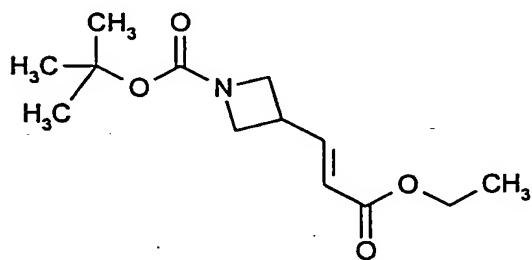
A solution of 3-hydroxymethylazetidine-1-carboxylic acid tert-butyl ester (3.0 g; 16.0 mmol) in methylene chloride (20 mL) was added dropwise to the reaction mixture.

- 5 Triethyl amine (11.1 mL; 80.1 mmol) was added and the reaction mixture was heated to room temperature. Methylene chloride (200 mL) and hydrochloric acid (200 mL; 1 N) was added. The aqueous phase was extracted with methylene chloride (100 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate (100 mL), dried (magnesium sulfate) and evaporated
- 10 in vacuo. The residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/heptane (4:1) as eluent to afford 1.11 g of 3-formylazetidine-1-carboxylic acid tert-butylester.

¹H-NMR (CDCl₃) δ : 1.43 (s, 9H); 3.37 (p, 1H); 4.05–4.15 (m, 4H); 9.82 (s, 1H).

15

3-((E)-2-Ethoxycarbonylvinyl)azetidine-1-carboxylic acid tert-butylester:



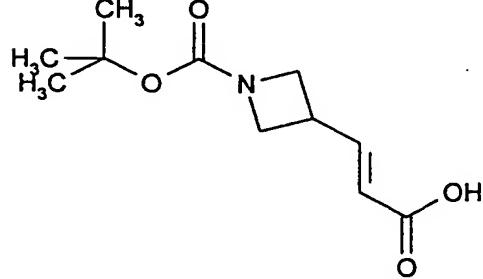
- 20 Triethyl phosphonoacetate (1.9 mL; 9.72 mmol) was dissolved in tetrahydrofuran (30 mL). Potassium tert-butoxide (1.1 g; 9.72 mmol) was added portionwise. 3-Formylazetidine-1-carboxylic acid tert-butyl ester (1.0 g; 5.40 mmol) was dissolved in tetrahydrofuran (6 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour at room temperature. Ethyl acetate (100 mL) and hydrochloric acid (100 mL; 1 N) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with saturated sodium hydrogen carbonate (100 mL),
- 25

dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/heptane (1:1) as eluent to afford 1.0 g of 3-((E)-2-ethoxycarbonylvinyl)azetidine-1-carboxylic acid tert-butyl ester.

5

¹H-NMR (CDCl₃) δ : 1.24 (t, 3H); 1.48 (s, 9H); 3.22-3.32 (m, 1H); 3.75 (dd, 2H); 4.08 (t, 2H); 4.15 (q, 2H); 5.8 (d, 1H); 7.02 (dd, 1H).

3-((E)-2-Carboxyvinyl)azetidine-1-carboxylic acid tert-butyl ester:



3-((E)-2-Ethoxycarbonylvinyl)azetidine-1-carboxylic acid tert-butyl ester (0.95 g;

3.72 mmol) was dissolved in 1,4-dioxane (15 mL). Lithium hydroxide (0.098 g; 4.1

15 mmol) and water (10 mL) were added. The reaction mixture was stirred for 12 hours at room temperature. Water (70 mL) was added and the reaction mixture was washed with tert-butyl methyl ether (70 mL) and the phases were separated. The aqueous phase was adjusted to pH 2 with an aqueous solution of sodium

hydrogensulfate (10 %) and extracted with tert-butyl methylether (3 x 70 mL). The

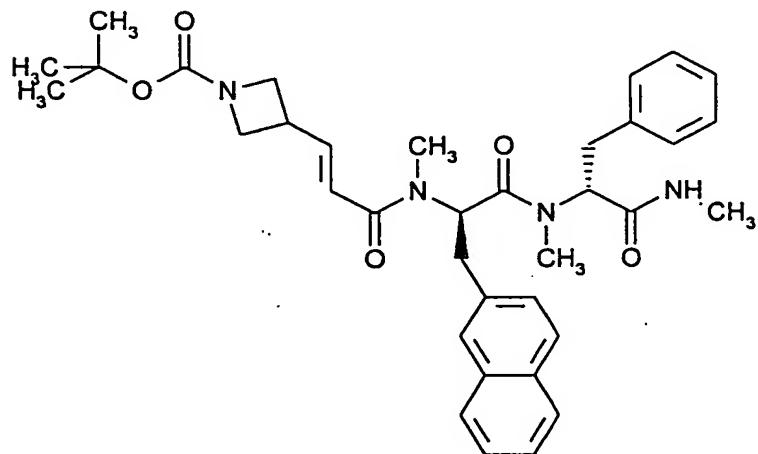
20 combined organic phases were dried (magnesium sulfate) and the solvent evaporated in vacuo to afford 0.76 g of 3-((E)-2-carboxyvinyl)azetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.43 (s, 9H); 3.31-3.42 (m, 1H); 3.84 (dd, 2H); 4.16 (t, 2H); 5.88

25 (d, 1H); 7.18 (dd, 1H).

3-(2-(Methyl-((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-

2-(2-naphthyl)ethyl)carbamoyl)vinyl)azetidine-1-carboxylic acid tert-butyl ester:



5 3-((E)-2-Carboxyvinyl)azetidine-1-carboxylic acid tert-butyl ester (0.28 g; 1.24 mmol) was dissolved in methylene chloride (3 mL). 1-Hydroxy-7-azabenzotriazole (0.17 g; 1.24 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g; 1.36 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. N-Methyl-2-methylamino-N-(1-(methyl-carbamoyl)-
10 2-phenylethyl)-3-(2-naphthyl)propionamide (0.50 g; 1.24 mmol) (prepared as in example 1) was dissolved in methylene chloride (3 mL) and added to the reaction mixture. Ethyldiisopropylamine (0.21 mL; 1.24 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (20 mL) was added and the reaction mixture was washed with water (10 mL), an aqueous
15 solution of sodium hydrogen sulfate (10 mL; 10 %), an aqueous solution of sodium hydrogen carbonate (10 mL; sat.) and water (10 mL). The organic phase was dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (2,5 x 20 cm) using 2.5%(7% ammonia in ethanol) in methylene chloride as eluent to afford 0.49 g of 3-((E)-2-(methyl((1R)-1-(methyl((1R)-1-
20 (methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)vinyl)azetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) d 1.41, 1.45 (two s, 9H); 1.55, 1.58 (two s, 3H); 2.21 (d, 1H); 2.54 (s, 1H); 2.72-2.81 (m, 3H); 2.83-2.96 (m, 1H); 3.0 (d, 3H); 3.02-3.42 (m, 3H); 3.68-

3.82 (m, 2H); 4.06 (q, 1H); 4.14 (q, 1H); 5.11, 5.31 (two m, 1H); 5.58, 5.88 (two dd, 1H); 6.03 (d, 1H); 6.88, 6.91 (two dd, 1H); 7.0-7.23 (m, 5H); 7.3-7.58 (m, 3H); 7.65-7.81 (m, 3H).

5 3-((E)-2-(Methyl((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)vinyl)azetidine-1-carboxylic acid tert-butyl ester (0.45 g; 0.73 mmol) was dissolved in methylene chloride (2 mL). Trifluoroacetic acid (2 mL) was added and the reaction mixture was stirred for 7 min. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (50 mL; pH 9) and sodium carbonate were added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.29 g of the title compound.

10

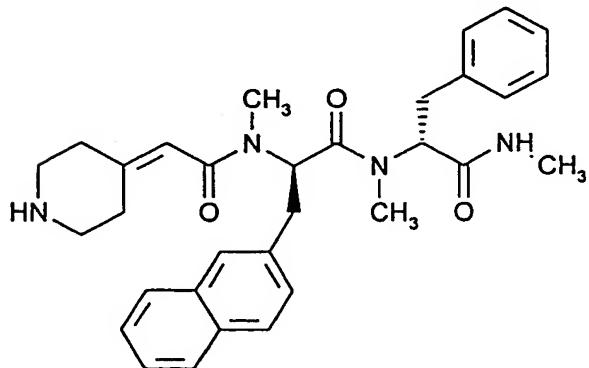
¹H-NMR (CDCl₃) d (selected peaks) : 2.25, 2.26, 2.28 (three s, 3H); 5.12, 5.31, 15 5.59, 5.88 (four dd, 2H); 6.00 (dd, 1H; J₁=15 Hz; J₂=2.5 Hz); 6.91 (m, 1H).

ESMS: m/z 513.2 (M+H)⁺

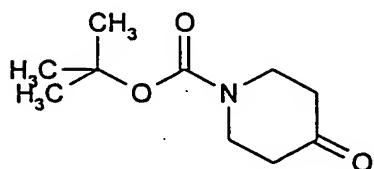
HPLC: r_t = 29.40 min (A1)

20 Example 7

(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(methyl((piperidin-4-ylidene)acetyl)amino)-3-(2-naphthyl)propionamide:



4-Oxopiperidine-1-carboxylic acid tert-butyl ester:



5

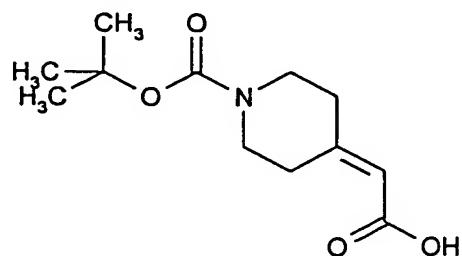
Piperidin-4-one hydrochloride (10.0 g; 74.3 mmol) was dissolved in tetrahydrofuran (100 mL) and an aqueous solution of sodium hydroxide (74 mL; 74.3 mmol; 1 N) was added. Di-tert-butyl dicarbonate (19.5 g; 89.2 mmol) was dissolved in

10 tetrahydrofuran (50 mL) and added dropwise. The reaction mixture was stirred for 12 hours at room temperature and evaporated in vacuo. The residue was extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with an aqueous solution of sodium hydrogen sulfate (100 mL; 10 %), dried (magnesium sulfate) and evaporated. The residue was crystallised from heptane and dried in vacuo to afford 10.9 g of 4-oxopiperidine-1-carboxylic acid tert-butyl ester.

15

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (s, 9H); 2.44 (t, 4H); 3.71 (t, 4 H).

20 4-Carboxymethylenepiperidine-1-carboxylic acid tert-butyl ester:



25 4-Oxopiperidine-1-carboxylic acid tert-butyl ester (8.0 g; 40.2 mmol) was dissolved in toluene (80 mL). Carboethoxymethylene triphenylphosphorane (17.5 g; 50.2

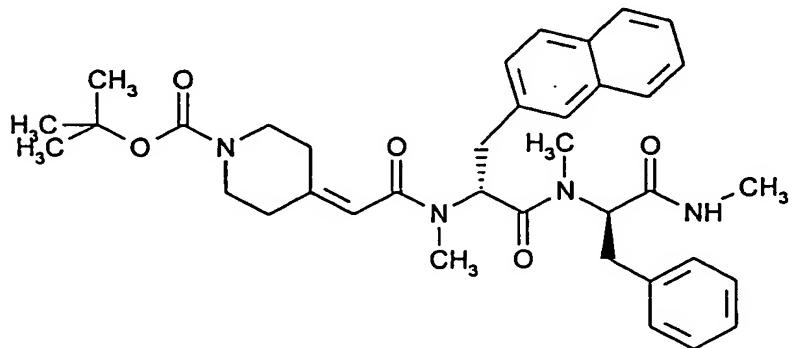
mmol) was added and the reaction mixture was heated 12 hours at reflux. The reaction mixture was evaporated in vacuo and the residue was chromatographed on silica (4.5 x 30 cm) using diethyl ether/heptane (1:1) as eluent to afford 9.5 g (35.7 mmol) of 4-Ethoxycarbonylmethylenepiperidine-1-carboxylic acid tert-butyl ester, which was dissolved in 1,4-dioxane and cooled to 0°C. Lithium hydroxide (2.73 g; 114 mmol) was dissolved in water (20 mL) and added. The reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (200 mL) and water (100 mL) was added. Sodium hydrogen sulfate (10 %; aqueous solution) was added to pH 2. The organic phase was washed with water (100 mL), dried (magnesium sulfate) and evaporated in vacuo to afford 5.49 g of 4-carboxymethylenepiperidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.47 (s, 9H); 2.31 (t, 2H), 2.94 (t, 2H); 3.50 (dt, 4H); 5.75 (s, 1H); 10.75 (s, 1H).

15

4-((N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methylene)piperidine-1-carboxylic acid tert-butyl ester:

20



4-Carboxymethylenepiperidine-1-carboxylic acid tert-butyl ester (0.60 g; 2.45 mmol) was dissolved in methylene chloride (50 mL) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g; 1.36 mmol) was added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-(methyl-carbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (0.5 g;

1.24 mmol, prepared as in example 1) was added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (50 mL; 10 %), an aqueous solution of sodium hydrogen carbonate (50 mL; sat.), dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (2 x 20 cm) using ethyl acetate as eluent to afford 0.270 g of 4-((N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methyl-carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methylene)piperidine-1-carboxylic acid tert-butyl ester.

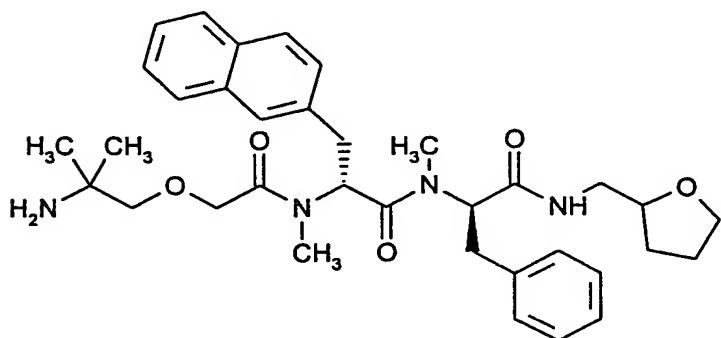
- 10 $^1\text{H-NMR}$ (CDCl_3) d : 1.42 (s, 3H); 1.45 (s, 3H); 1.52, 1.55 (two s, 9H); 2.05-2.18 (m, 1H); 2.34-2.42 (m, 2H); 2.71-2.80 (m, 3H); 2.80-2.89 (m, 1H); 2.90-3.01 (m, 3H); 3.02-3.36 (m, 3H); 5.16, 5.36 (two m, 1H); 5.57, 5.90 (two t, 1H); 6.90-7.25 (m, 6H); 7.28-7.53 (m, 3H); 7.61-7.82 (m, 3H).
- 15 4-((N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methylene)piperidine-1-carboxylic acid tert-butyl ester (0.27 g; 0.43 mmol) was dissolved in methylene chloride (8 mL) and trifluoroacetic acid (8 mL) was added. The reaction mixture was stirred for 10 min. Methylene chloride (30 mL) and an aqueous solution of sodium hydrogen carbonate (10 mL; saturated) were added. Solid sodium hydrogen carbonate was added to pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.17 g of the title compound.
- 25 $^1\text{H-NMR}$ (CDCl_3) d (rotamers, selected peaks): 5.18; 5.38; 5.58; 5.90 (four dd, 2H); 5.49, 5.52 (two s, 1H)

ESMS: m/z 527.4 ($\text{M}+\text{H})^+$

- 30 HPLC: $r_t = 28.62$ min (Method A1)

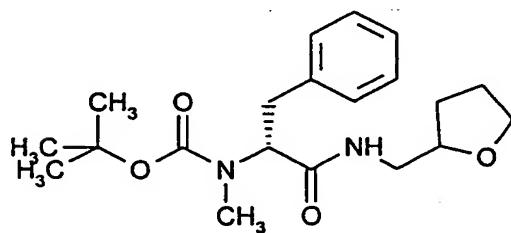
Example 8

5 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide:



10

Methyl-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)-carbamoyl)ethyl)carbamic acid tert-butyl ester:

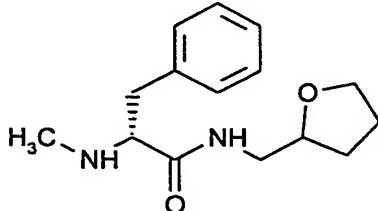


15 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-phenylpropionic acid (5.0 g; 17.9 mmol) was dissolved in methylene chloride (50 mL). 1-Hydroxybenzotriazole (2.42 g; 17.9 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.58 g; 18.8 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. ((Tetrahydrofuran-2-yl)methyl)amine (1.72 g; 17.1 mmol) and 20 diisopropyl- ethylamine (3.2 mL; 18.8 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (200 mL) was added and the reaction mixture was washed with water (100 mL), an aqueous

solution of sodium hydrogen sulfate (10 %, 100 mL), an aqueous solution of sodium hydrogen carbonate (saturated, 100 mL), water (100 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (2:1) as eluent to afford 5.62 g of
 5 methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.28; 1.38 (two s, 9H); 1.40-1.57 (m, 1H); 1.76-2.01 (m, 3H);
 2.70-2.80 (m, 3H); 2.86-2.96 (m, 1H); 3.15-3.61 (m, 3H); 3.67-3.75 (m, 1H); 3.76-
 10 3.85 (m, 1H); 3.86-3.99 (m, 1H); 4.72; 4.92 (two m, 1H); 6.26; 6.4 (two m, 1H);
 7.14-7.29 (m, 5H).

(2R)-2-Methylamino-3-phenyl-N-((2-tetrahydrofuranyl)methyl)propionamide:



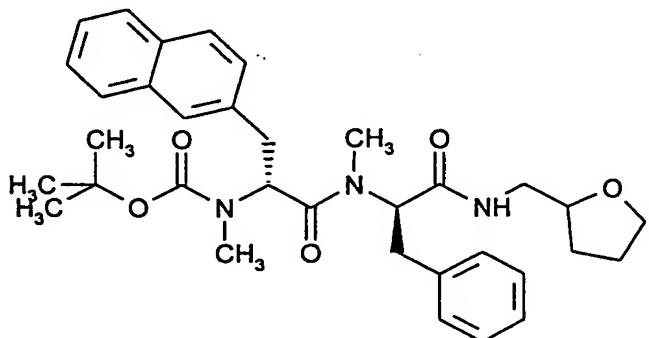
Methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamic acid tert-butyl ester (5.5 g; 15.2 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid (20 mL) was added. The reaction mixture was stirred for 1 hour at room temperature. Methylenec chloride (100 mL) and an aqueous solution of
 20 sodium hydrogen carbonate/sodium carbonate (pH 9, 50 mL) were added and solid sodium hydrogen carbonate was added until pH 8. The aqueous phase was extracted with methylene chloride (100 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to afford 3.62 g of (2R)-2-Methyl-amino-3-phenyl-N-((2-tetrahydrofuranyl)methyl)propionamide.

25

¹H-NMR (CDCl₃) δ : 1.46-1.57 (m, 1H); 1.62 (s, 1); 1.82-2.01 (m, 3H); 2.29 (d, 3H);
 2.65-2.74 (m, 1H); 3.16-3.27 (m, 3H); 3.49-3.58 (m, 1H); 3.7-3.78 (m, 1H); 3.8-3.88 (m, 1H); 3.9-3.98 (m, 1H); 7.19-7.34 (m, 5H); 7.43 (s, 1H).

Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)-carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester:

5



(2R)-2-(tert-Butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (4.14 g; 12.58 mmol) was dissolved in methylene chloride (40 mL). 1-Hydroxy-7-

azabenzotriazole (1.71 g; 12.6 mmol) and N-(3-dimethylaminopropyl)-N'-

- 10 ethylcarbodiimide hydrochloride (2.52 g; 13.2 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-2-Methylamino-3-phenyl-N-((2-tetrahydrofuranyl)methyl)propionamide (3.0 g; 11.4 mmol) and diisopropylethylamine (2.15 mL; 12.6 mmol) were added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (200 mL) was added.
- 15 The reaction mixture was washed with water (200 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9, 100 mL), an aqueous solution of sodium hydrogen sulfate (10 %, 100 mL), water (100 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 40 cm) using ethyl acetate/heptane (1:1) as eluent
- 20 to afford 4.27 g of methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)-carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester.

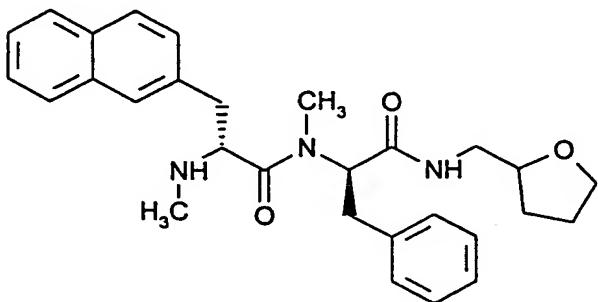
¹H-NMR (CDCl₃) δ : 1.01 (s, 2H); 1.24 and 1.27 (two s, 9H); 1.54-1.64 (m, 1H);

- 25 1.65-1.99 (m, 2H); 2.24 (t, 2H); 2.7-2.8 (m, 1H); 2.82; 2.88 (two d, 3H); 2.95 (s, 3H);

L
E
B
B
S
S
S
C
C
C
C
R

3.00-3.44 (m, 2H); 2.45-2.98 (m, 3H); 4.96-5.10 (m, 1H); 5.30-5.45 (m, 1H); 5.95; 6.17 (two m, 1H); 7.02-7.10 (m, 1H); 7.11-7.23 (m, 4H); 7.34-7.47 (m, 3 H); 7.65 (s, 1H); 7.68-7.8 (m, 4H).

5 (2R)-N-Methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)propionamide:

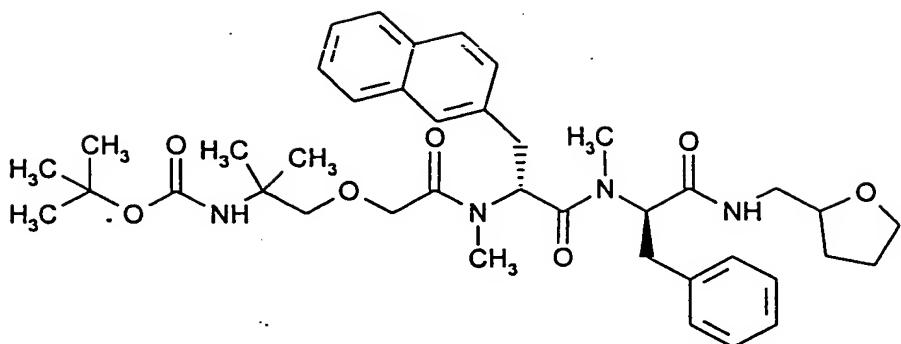


Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)-
10 carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester. (4.2
g; 7.32 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid
(20 mL) was added. The reaction mixture was stirred for 15 min at room
temperature. Methylene chloride (100 mL), an aqueous solution of sodium
hydrogen carbonate/sodium carbonate (pH 9, 100 mL) and solid sodium hydrogen
15 carbonate were added to the reaction mixture until pH 8. The organic phase was
dried (magnesium sulfate) and evaporated in vacuo to afford 3.5 g of (2R)-N-
methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-
yl)methyl)carbamoyl)ethyl)propionamide.

20

(1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)-
ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butyl ester:

10062891 · 020502



(2-tert Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.5 g; 2.06 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.2 g; 1.51 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.30 g; 1.58 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)propionamide (0.65 g; 1.37 mmol) and diisopropylethylamine (0.26 mL; 1.51 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (100 mL) was added. The reaction mixture was washed with an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate (sat; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was filtered through silica to afford 0.76 g of (1,1-dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 0.89-0.95 (m, 3H); 1.1; 1.15 (two s, 3H); 1.41; 1.43 (two s, 9H); 1.68-2.0 (m, 4H); 2.22 (s, 1H); 2.26 (s, 1H); 2.82; 2.86 (two d, 3H); 2.88-2.97 (m, 2H); 2.99 (d, 3H); 3.06-3.36 (m, 3H); 3.45-3.95 (m, 5H); 5.05; 5.16 (two m, 1H); 5.33 (s, 1H); 5.37-5.5 (m, 1H); 5.81; 5.91 (two q, 1H); 6.89-7.1 (m, 2H); 7.13-7.24 (m, 4H); 7.34-7.47 (m, 3H); 7.63 (s, 1H); 7.69-7.79 (m, 3H).

(1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butyl ester (0.76 g; 1.08 mmol) was dissolved in methylene chloride (5 mL) and trifluoroacetic acid (5 mL)

5 was added. The reaction mixture was stirred for 10 min at room temperature.

Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and solid sodium hydrogen carbonate was added to the reaction mixture until pH 8. The aqueous phase was extracted with methylene chloride (2 x 50 mL) and the combined organic layers were dried 10 (magnesium sulfate) and evaporated in vacuo to afford 0.6 g of the title compound.

¹H-NMR (CDCl₃) d (rotamers; selected peaks) : 1.00; 1.02; 1.03; 1.09 (four s; 6H); 5.07; 5.15; 5.78; 5.97 (four dd, 1H); 5.42 (m; 1H).

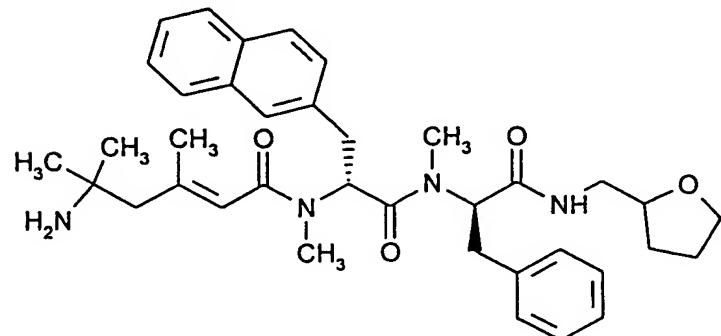
15 ESMS: m/z 602.9 (M+H)⁺

HPLC: R_t = 33.30 (Method A1)

Example 9

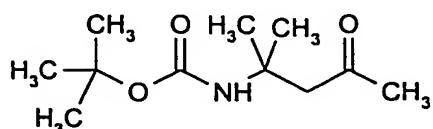
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(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((2-tetra-hydrofuranyl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



25

(1,1-Dimethyl-3-oxobutyl)carbamic acid tert-butylester:



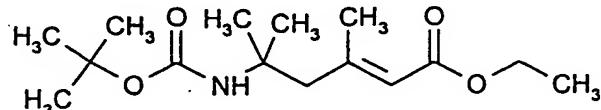
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Diacetonamine hydrogen oxalate (30.0 g; 146 mmol) was suspended in tetrahydrofuran (400 mL). An aqueous solution of sodium hydroxide (1 N; 146 mL) was added. Di-tert-Butyl dicarbonate (38.3 g; 175 mmol) was dissolved in tetrahydrofuran (100 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred for 2 hours at room temperature. Sodium hydroxide (1 N; 146 mL) was added and the reaction mixture was stirred for 12 hours at room temperature. Water (200 mL) and ethyl acetate (200 mL) were added. The aqueous phase was extracted with ethyl acetate (4 x 200 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed in vacuo. The residue was chromatographed on silica (6 x 40 cm) using ethyl acetate/heptane (1:3) as eluent to afford 28.4 g of (1,1-dimethyl-3-oxobutyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ 1.34 (s, 6H); 1.42 (s, 9H); 2.14 (s, 3H); 2.86 (s, 2H); 4.85 (s, 1H).

20

(E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid ethylester:



25

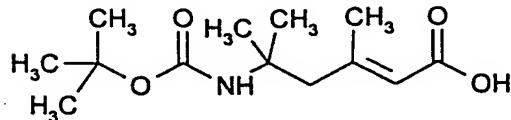
Triethyl phosphono acetate (4.7 g; 20.9 mmol) was dissolved in tetrahydrofuran (36 mL). Potassium tert-butoxide (2.3 g; 20.9 mmol) was added and the reaction mixture was stirred for 40 min at room temperature.

(1,1-dimethyl-3-oxobutyl)carbamic acid tert-butylester (2.5 g; 11.6 mmol) was dissolved in tetrahydrofuran (15 mL) and added dropwise to the reaction mixture which was heated to reflux for 12 h. Ethyl acetate (100 mL) and hydrochloric acid (1 N; 100 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with an aqueous solution of sodium hydrogen carbonate (saturated; 100 mL), dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (1:2) as eluent to afford 2.0 g of (E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid ethylester.

¹H-NMR (CDCl₃) δ 1.25 (t, 3H); 1.30 (s, 6H); 1.44 (s, 9H); 2.21 (s, 3H); 2.58 (s, 2H); 4.14 (q, 2H); 4.48 (s, 1H); 5.65 (s, 1H).

15

(2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid:



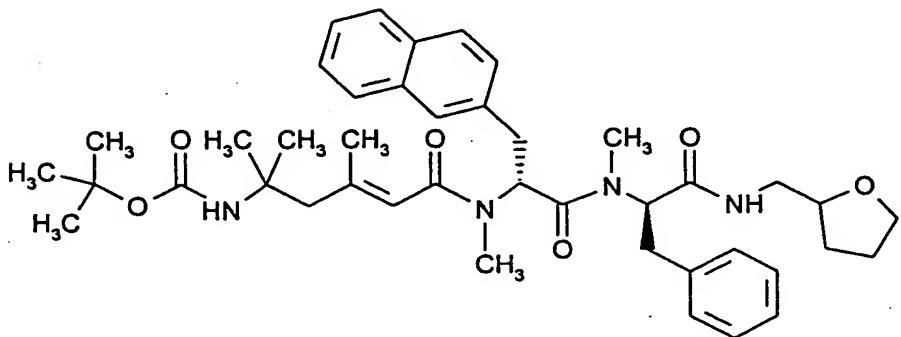
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(E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid ethylester (1.95 g; 6.83 mmol) was dissolved in 1,4-dioxane (25 mL) and water (15 mL). Lithium hydroxide (0.18 g; 7.52 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Water (150 mL) and tert-butyl methyl ether (150 mL) was added. The aqueous phase was diluted with an aqueous solution of sodium hydrogensulfate (10 %) until pH 2,5 and extracted with tert-butyl methylether (3 x 100 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo. The residue was recrystallized from heptane (20 mL) to afford 0.6 g of (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid.

30

¹H-NMR (CDCl₃) δ 1.29 (s, 6H); 1.44 (s, 9H); 2.23 (s, 3H); 2.62 (s, 2H); 4.45 (s, 1H); 5.66 (s, 1H).

5 ((3E)-1,1,3-Trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
ethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)-
ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester:



10 (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid (0.3 g; 1.17 mmol)
was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.12 g; 0.85 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.89 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

15 (2R)-N-Methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)propionamide (0.37 g; 0.78 mmol) and diisopropylethylamine (0.15 mL; 0.85 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), water (30 mL), and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2.5 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.21 g of ((3E)-1,1,3-trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
ethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)-ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester.

20 ((3E)-1,1,3-trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
ethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)-ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester:
25 ((3E)-1,1,3-trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-

naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butylester.

¹H-NMR (CDCl₃)(rotamers; selected peaks) d : 1.15; 1.21; (two s; 6H); 1.30; 1.41 (two s; 9H).

5

((3E)-1,1,3-Trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butylester (0.20 g; 0.28 mmol) was dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 6 min at room temperature. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and solid sodium hydrogen carbonate were added to the reaction mixture to pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.155 g of the title compound.

¹H-NMR (CDCl₃)(rotamers; selected peaks) d : 1.36; 1.41 (two s; 6H); 4.38; 5.12; 5.31; 6.25 (four m; 2H).

20

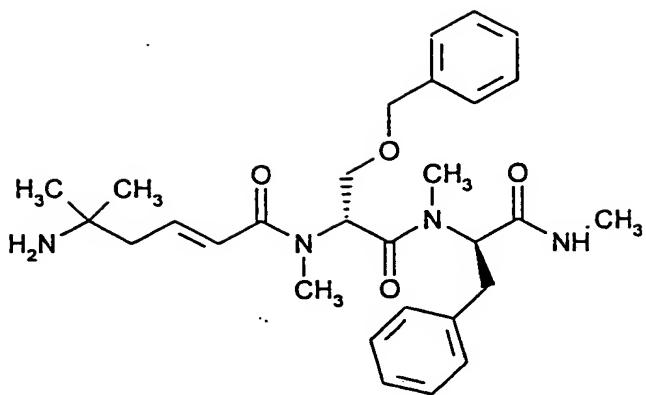
ESMS: m/z : 613.7 (M+H)⁺

HPLC: R_t = 34.47 (Method A1)

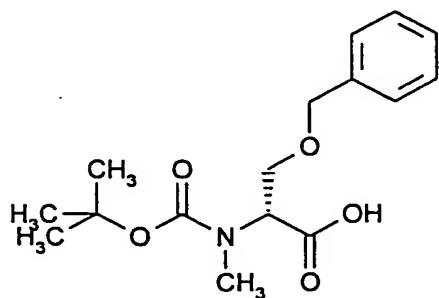
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Example 10

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide:



(2R)-3-Benzyl-2-(tert-butoxycarbonylmethylamino)propionic acid:



5

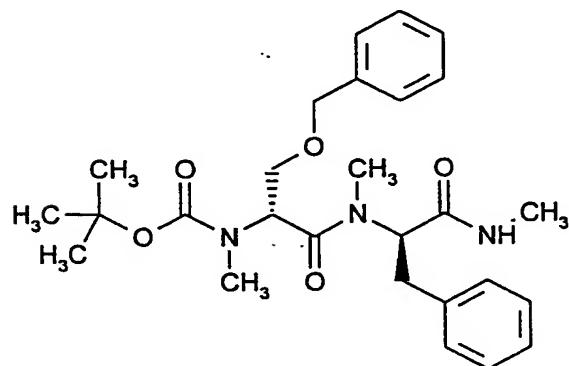
(2R)-3-Benzyl-2-(tert-butoxycarbonylmethylamino)propionic acid (7.0 g; 23.7 mmol) was dissolved in dry tetrahydrofuran and iodomethane (11.9 mL; 189 mmol) was added. The reaction mixture was cooled to 0°C and sodium hydride (60 % in mineral oil) 10 (2.73 g; 71 mmol) was added. The reaction mixture was left 3 days without stirring at 0°C. Citric acid (5 %) was added until pH 2.5. Tetrahydrofuran was removed in vacuo and the residue was extracted with methylene chloride (3 x 100 mL). The organic phase was dried (magnesium sulfate) and evaporated in vacuo. The residue was dissolved in diethyl ether (20 mL) and dicyclohexylamine (10 mL) and 15 heptane (100 mL) were added. The reaction mixture was left 3 days without stirring at 0°C. The reaction mixture was filtered to afford 5.78 g of (2R)-3-benzyl-2-(tert-butoxycarbonylmethylamino)propionic acid.

¹H-NMR (CDCl₃) δ 1.40; 1.42 (two s, 9H); 2.91; 2.97 (two s, 3H); 3.90, 3.91 (two s,

2H); 4.55 (two d, 2H); 3.83; 4.90 (two t; 1H); 7.25-7.38 (arom. 5H).

N-((1R)-2-Benzyl-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamic acid tert-butyl ester:

5



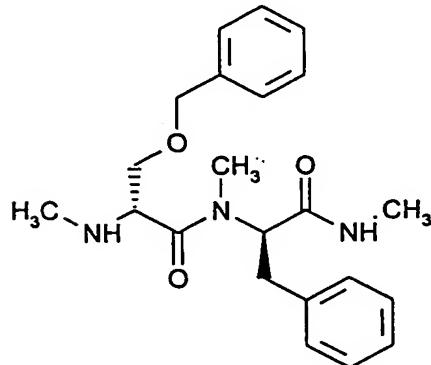
(2R)-3-Benzyl-2-(tert-butoxycarbonylmethylamino)propionic acid (0.39 g; 1.25 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.16 g; 1.14 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide

10 hydrochloride (0.23 g; 1.20 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

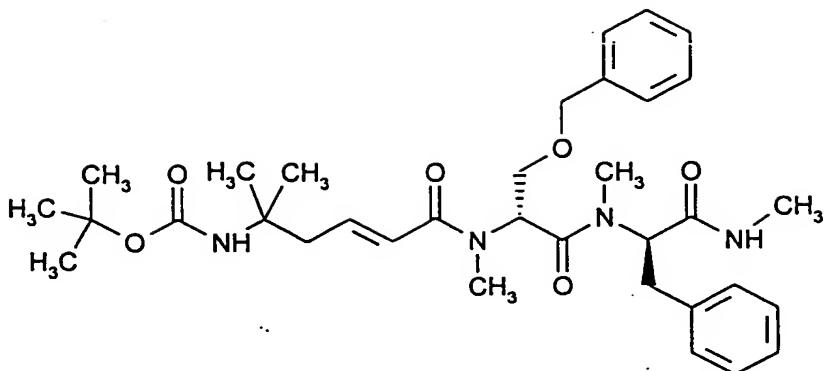
N-methyl-2-methylamino-3-phenyl-propionamide (0.2 g; 1.04 mmol, prepared as in example 1) and diisopropylethylamine (0.2 mL; 1.14 mmol) were added and the 15 reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was added. The reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate (saturated, 30 mL), an aqueous solution of sodium hydrogen sulfate (10 %, 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was 20 chromatographed on silica (2.5 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.241 g of N-((1R)-2-benzyl-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) (selected peaks) d 1.42; 1.45 (two s; 9H); 2.71; 2.78 (two d, 3H); 25 2.84; 2.92 (two s; 3H); 4.11; 4.30 (two d; 1H); 4.43; 4.57 (two t; 1H)

(2R)-3-Benzyl-N-methyl-2-(methylamino)-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)propionamide:



- 5 N-((1R)-2-Benzyl-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)ethyl)N-methylcarbamic acid tert-butyl ester (0.23 g; 0.476 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred for 10 min at room temperature. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.182 g of (2R)-3-Benzyl-N-methyl-2-(methylamino)-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)propionamide.
- 10 ¹H-NMR (CDCl₃) (selected data for major rotamer) d 2.18 (d, 3H); 2.92-2.95 (d and s, 6H); 3.31-3.45 (m, 4H); 3.65 (t, 1H); 4.45 (d, 1H); 4.48 (d, 1H); 4.65 (dd, 1H).
- 15 ((3E)-4-(N-((1R)-2-Benzyl-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester:
- 20



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.12 g; 0.49 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.07 g; 0.49 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.1 g; 0.51 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-3-Benzyl-N-methyl-2-(methyl-amino)-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-propionamide (0.17 g; 0.44 mmol) and diisopropylethylamine (0.084 mL; 0.49 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was extracted with an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2.5 x 30 cm) using methylene chloride/ethyl acetate (1:1) as eluent to afford 0.275 g of ((3E)-4-(N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) (selected data for major rotamer) d 1.25 (s, 3H); 1.27 (s, 3H); 1.41 (s, 9H); 2.05 (s, 3H); 2.78 (d, 3H); 3.07 (s, 3H); 4.32 (d, 1H); 4.41 (d, 1H); 5.05 (dd, 1H); 5.51 (dd, 1H); 6.30 (d; J=17 Hz; 1H); 6.79 (m, 1H).

((3E)-4-(N-((1R)-2-Benzyloxy-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic

acid tert-butyl ester (0.275 g; 0.452 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 7 min at room temperature. Methylene chloride (30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.13 g of the title compound.

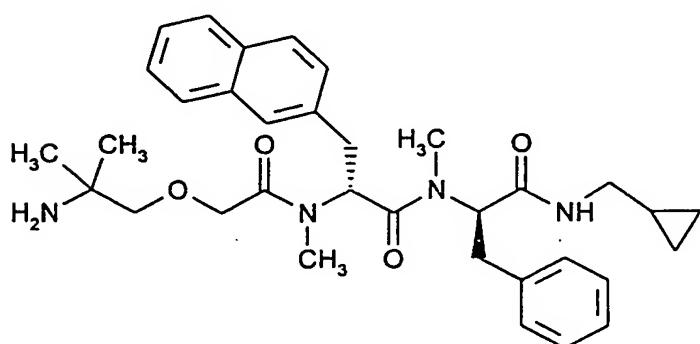
¹H-NMR (CDCl₃) (selected data for major rotamer) d 1.27 (s, 3H); 1.28 (s; 3H); 2.84 (d, 3H); 2.95 (s, 3H); 3.08 (s, 3H); 4.32 (d; 1H); 4.40 (d, 1H); 5.12 (dd, 1H); 6.34 (d, J=18Hz, 1H).

ESMS: m/z 509.7 (M+H)⁺

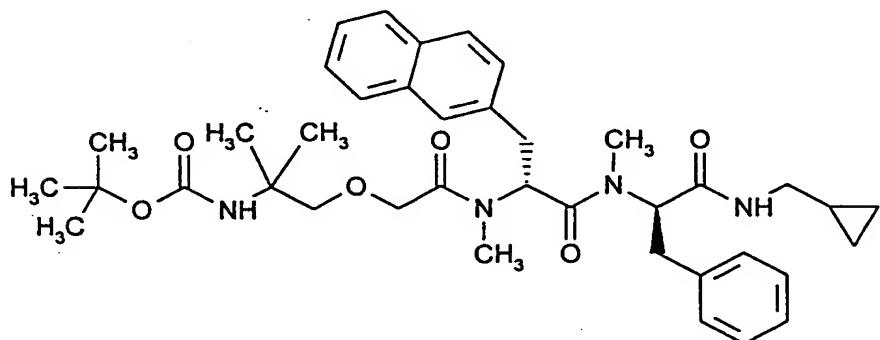
HPLC: R_t = 23.45 min (Method A1)

Example 11

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-1-((cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)-propionamide:



(2-((N-((1R)-1-(N-((1R)-1-(Cyclopropylmethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester:



5 (2-tert-Butoxycarbonylamino-2-methylpropoxy) acetic acid (0.36 g; 1.49 mmol) was dissolved in methylene chloride (5 mL). 1-Hydroxy-7-azabenzotriazole (0.2 g; 1.49 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.3 g; 1.56 mmol) were added and the reaction mixture was stirred for 15 min at room
10 temperature.

10 (2R)-N-((1R)-1-((Cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.60 g; 1.35 mmol) and diisopropylethylamine (0.26 mL; 1.49 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was
15 added. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3.5 x 40 cm) using ethyl acetate/heptane (1:1) as eluent to afford 0.64 g of (2-((N-((1R)-1-(N-
20 ((1R)-1-((cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) (rotamers, selected peaks) δ : -0.11 (m 1H); 0.19 (m, 1H); 0.45
25 (m, 1H); 0.95; 1.17; 1.25; 1.27; 1.40; 1.43; 1.58 (seven s, 15H); 2.29; 2.81; 2.91;

3.03 (four s, 6H).

(2-((N-((1R)-1-(N-((1R)-1-((Cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)methoxy)-1,1-di-
5 methylethyl)carbamic acid tert-butylester (0.64 g; 0.951 mmol) was dissolved in
methylen chloride (3 mL) and trifluoroacetic acid (3 mL) was added. The reaction
mixture was stirred for 5 min. Methylen chloride (25 mL), an aqueous solution of
sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen
carbonate (solid) were added to the reaction mixture to pH 8. The organic phase
10 was dried (magnesium sulfate) and evaporated in vacuo to afford 0.48 g of the title
compound.

¹H-NMR (CDCl₃) (rotamers, selected peaks) δ : 0.55; 0.57; 0.80; 0.82 (four s, 6H);
2.09; 2.62; 2.75; 2.84 (four s; 6H); 3.68; 3.82 (two d, 2H together with a singlet at
15 3.69); 4.92; 5.22; 5.30; 5.38; 5.65 (five dd, 3H);

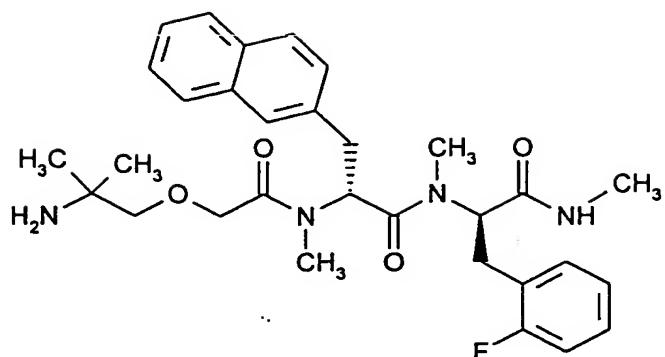
ESMS: m/z 572.0 (M+H)⁺

HPLC: R_t = 35.52 min (Method A1)

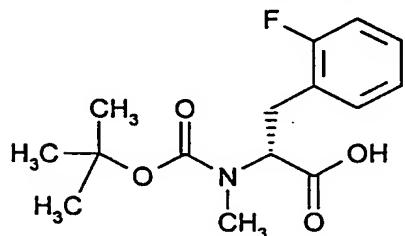
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Example 12

(2R)-2-(((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(2-fluorophenyl)-
25 1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:



(2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-fluorophenyl)propionic acid:



(The N-methylation in this and other examples in this invention may be performed as in Can. J. Chem. 1977, 55, 906).

10

(2R)-2-tert-Butoxycarbonylamino-3-(2-fluorophenyl)propionic acid (5.0 g; 17.5 mmol) was dissolved in dry tetrahydrofuran. Iodomethane (7.2 mL; 115 mmol) was added and the reaction mixture was cooled to 0°C. Sodium hydride (60% susp. in oil; 1.41 g; 42.0 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise. The ethyl acetate was removed in vacuo and the residue was diluted with ether (30 mL) and water (100 mL). The organic phase was extracted with an aqueous solution of sodium hydrogen carbonate (aqueous; 50 mL). To the combined aqueous layers was added citric acid (5 %) until pH 3 and ethyl acetate (3 x 50 mL) was added and the phases were separated. The combined organic layers were washed with water (2 x 50 mL), an aqueous solution of sodium

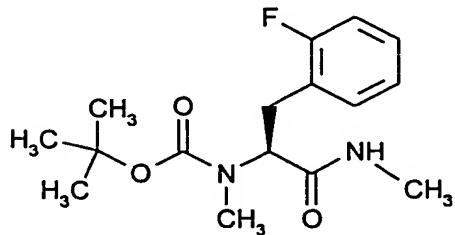
PCT/CA97/00120

thiosulfate (5 %; 2 x 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was dissolved in diethyl ether (10 mL). Dicyclohexylamine (9.0 mL) was added. The reaction mixture was filtered to afford 5.57 g of (2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-2-fluorophenyl)propionic acid as a dicyclohexylammonium salt.

¹H-NMR (CDCl₃) δ 1.27; 1.35 (two s, 9H); 2.21; 2.25 (two s, 3H); 3.03 (m, 2H); 4.26; 4.37 (two dd, 1H); 6.9-7.3 (arom 4H).

10

N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamic acid tert-butylester:



15

(2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-fluorophenyl)propionic acid as a dicyclohexylammonium salt (5.57 g; 18.73 mmol) was dissolved in methylene chloride (30 mL) and washed with an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL). The organic phase was dried (magnesium sulfate) and filtered.

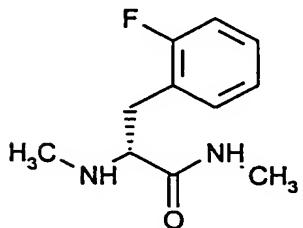
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Hydroxybenzotriazole hydrate (2.53 g; 18.73 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.75 g; 19.6 mmol) were added to the filtrate and the mixture was stirred for 15 min at room temperature. Methylamine (40% in methanol; 0.53 g; 17.0 mmol) and diisopropylethylamine (3.2 mL; 18.7 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (50 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3.5 x 40 cm) using ethyl

acetate/heptane (2:1) as eluent to afford 2.4 g of N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamic acid tert-butyl ester.

H-NMR (CDCl₃) d : 1.25; 1.35; 1.38 (three s, 9H); 2.74 (s, 3H); 2.75 (d, 3H); 2.80-5 3.55 (m, 2H); 4.35; 4.82; 5.00; 5.12 (four dd; 6.9-7.3 (arom, 4H).

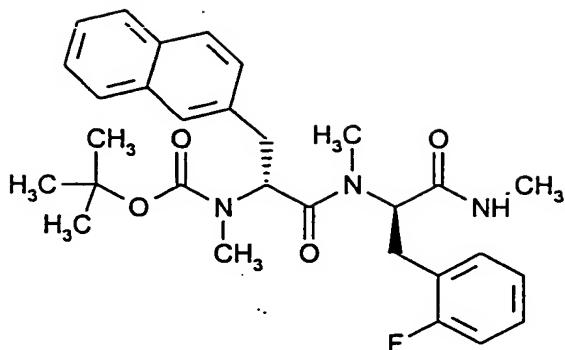
(2R)-3-(2-Fluorophenyl)-N-methyl-2-(methylamino)-propionamide:



10 N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamic acid
tert-butylester (2.4 g; 7.73 mmol) was dissolved in methylene chloride.
Trifluoroacetic acid (10 mL) was added and the reaction mixture was stirred for 30
min at room temperature. Methylene chloride (30 mL), an aqueous solution of
sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen
15 carbonate (solid) were added to the reaction mixture until pH 8. The organic phase
was dried (magnesium sulfate) and evaporated in vacuo to afford 1.1 g of
(2R)-3-(2-fluorophenyl)-N-methyl-2-(methylamino)- propionamide.

20 H-NMR (CDCl₃) d 2.31 (s, 3H); 2.80 (d, 3H); 2.86 (dd, 1H); 3.17 (dd, 1H); 3.28
(dd, 1H); 7.0-7.30 (arom. 4H).

N-((1R)-1-(N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-
25 methylcarbamoyl)-2-(2-naphthyl)-ethyl)-N-methylcarbamic acid tert-butyl ester.

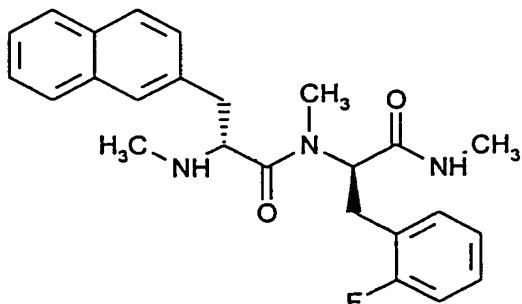


Tert-Butoxycarbonylaminoacetic acid (0.18 g; 2.39 mmol) was dissolved in methylene chloride (20 mL). 1-Hydroxybenzotriazole (0.32 g; 2.39 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.55 g; 2.87 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

(2R)-3-(2-Fluorophenyl)-N-methyl-2-(methylamino)propionamide (1.0 g; 4.78 mmol) and diisopropylethylamine (0.9 mL; 5.26 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. A mixture of 2-(tert-butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (0.78 g; 2.39 mmol), 1-hydroxy-7-azabenzotriazole (0.33 g; 2.39 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.55 g; 2.87 mmol) were dissolved in methylene chloride (20 mL) and added to the reaction mixture. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2.5 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.86 g of N-((1R)-1-(N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methyl-carbamic acid tert-butylester.

H-NMR (CDCl₃) (selected peaks, rotamers) d : 1.34 (s, 9H); 2.35 (s, 3H); 2.78 (s, 3H); 5.03-5.45 (four m, 2H).

(2R)-N-((1R)-2-(2-Fluorophenyl)-1-methylcarbamoylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide:



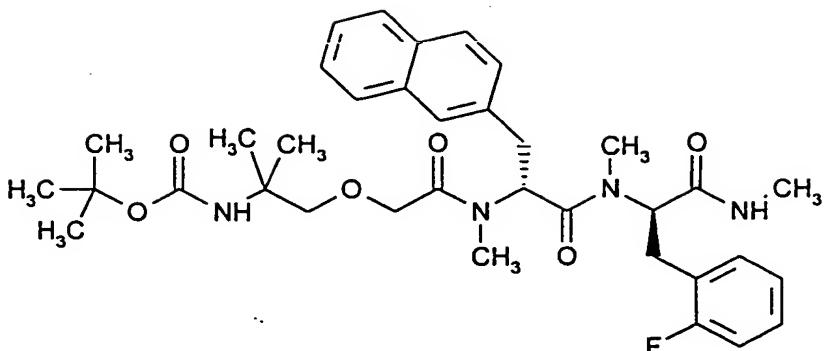
5

N-((1R)-1-(N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester (0.85 g; 1.63 mmol) was dissolved in methylene chloride (5 mL). Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 15 min at room temperature.

- 10 Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.669 g of (2R)-N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.
- 15

H-NMR (CDCl_3) (selected peaks, rotamers) d : 2.02 (d, 3H); 2.57 (s, 3H); 3.78 (dd, 1H); 5.55 (dd, 1H)

- 20 (2-(((1R)-1-(((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butyl ester:



(2-tert-Butoxycarbonylamino-2-methylpropoxy) acetic acid (0.19 g; 0.78 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.12 g; 5 0.86 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.90 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.33 g; 0.78 mmol) and diisopropylethylamine (0.17 mL; 0.86 mmol) were added and the reaction mixture 10 was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 50 mL), water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.47 g of 15 (2-(((1R)-1-(((1R)-2-(2-fluorophenyl)-1-methylcarbamoyl-ethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)methyl-carbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butyl ester.

H-NMR (CDCl_3) (rotamers, selected peaks for major isomer) d 1.03 (s, 3H) ; 1.06 20 (s, 3H); 2.78 (s, 3H); 2.80 (d, 3H); 3.98 (s, 3H); 4.95 (d, 1H); 5.00 (d, 1H); 5.70 (dd, 1H), 5.85 (dd, 1H).

(2-(((1R)-1-(((1R)-2-(2-Fluorophenyl)-1(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid 25 tert-butyl ester (0.46 g; 0.707 mmol) was dissolved in methylene chloride (3 mL).

Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 8. The organic phase 5 was dried (magnesium sulfate) and evaporated in vacuo to afford 0.275 g of the title compound.

H-NMR (CDCl_3) (selected peaks, rotamers) d : 0.76; 0.99 (two d, 6H); 2.30; 2.80 (two d, 3H); 2.47; 2.78; 2.94; 2.97 (four s, 6H); (3.90 (d), 3.94(s), 4.05 (d), 2H);
10 5.27; 5.37; 5.67; 5.86 (four dd, 2H); 6.96-7.82 (arom. 12H).

PDMS : m/z 550.7 ($\text{M}+\text{H})^+$

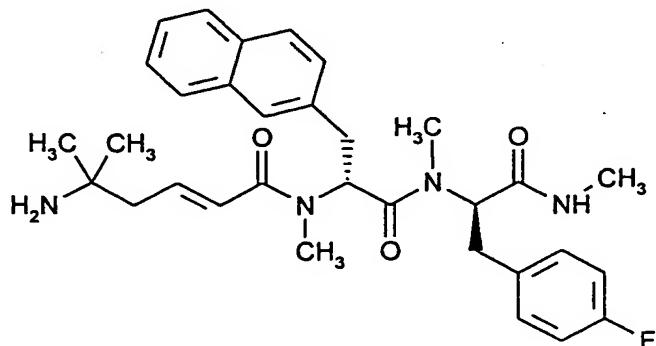
HPLC: $R_t = 31.28$ min (Method A1)

15

Example 13

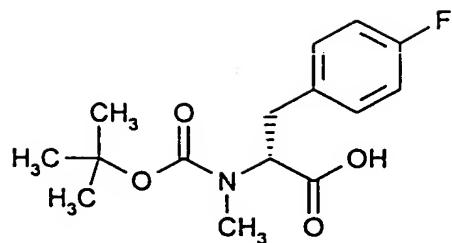
(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide:

20



(R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid:

25

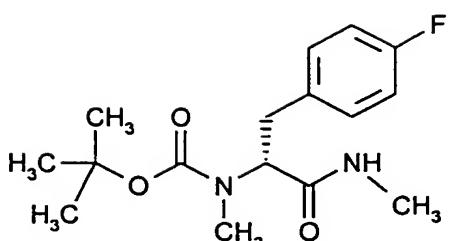


SYNTHETIC
ROUTE
B

2-tert-Butoxycarbonylamino-3-(4-fluorophenyl)propionic acid (5.0 g; 17.7 mmol) was dissolved in dry tetrahydrofuran. Iodomethane (8.8 mL; 141 mmol) was added and 5 the reaction mixture was cooled to 0°C. Sodium hydride (2.1 g; 53.0 mmol) was slowly added and the reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise to the reaction mixture. The ethyl acetate was removed in vacuo and the residue was diluted with diethyl ether (30 mL) and water (100 mL). The organic 10 phase was extracted with a saturated aqueous solution of sodium hydrogen carbonate (50 mL). Citric acid (5 %) was added to the combined aqueous phases until pH 3, which were then extracted with ethyl acetate (2×50 mL) and the phases were separated. The organic phase was washed with water (2×50 mL), an aqueous solution of sodium thiosulfate (5 %; 2×50 mL) and water (50 mL) and 15 dried (magnesium sulfate). The solvent was removed in vacuo and the residue was dissolved in diethyl ether (10 mL). Dicyclohexylamine (10 mL) was added. Methylene chloride (30 mL) was added and the mixture was heated until the precipitate was dissolved. Diethyl ether (20 mL) and heptane (20 mL) were added and the reaction mixture was left 12 hours without stirring. The reaction mixture was 20 filtered to afford 5.7 g of (R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid as a dicyclohexylammonium salt.

¹H-NMR (CDCl_3) (mixture of rotamers) δ : 1.21; 1.31 (two s, 9H); 2.75; 2.84 (two s, 3H); 2.86-3.02 (m, 1H); 3.28-3.42 (m, 1H); 4.65; 4.85 (two dd, 1H); 6.85-7.00 (m, 2H); 7.10-7.25 (m, 2H).

((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester:



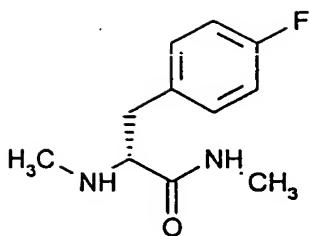
The dicyclohexylammoniumsalt of

- 5 (R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid (3.00 g; 10.1 mmol) was dissolved in methylene chloride (30 mL) and washed with an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL). The organic phase was dried (magnesium sulfate) and filtered. 1-Hydroxybenzotriazole (1.40 g; 10.1 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.0 g; 10.6 mmol) were added to the filtrate and the reaction mixture was stirred for 15 min at room temperature. Methylamine (40 % in methanol; 0.75 g; 9.17 mmol) and diisopropylethylamine (1.7 mL; 10.1 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (sat; 50 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.06 g of ((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester.

20

$^1\text{H-NMR}$ (CDCl_3) δ : 1.29; 1.37 (two s, 9H); 2.74 (s, 3H); 2.8 (s, 3H); 2.82-2.95 (m, 1H); 3.36-3.48 (m, 1H); 4.63; 4.86 (m, 1H); 5.89; 6.14 (two s, 1H); 6.9-7.0 (m, 2H); 7.1-7.21 (m, 2H).

25 (2R)-3-(4-Fluorophenyl)-N-methyl-2-(methylamino)propion-amide:



((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamic acid

tert-butylester (1.0 g; 3.22 mmol) was dissolved in methylene chloride (5 mL).

Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 30

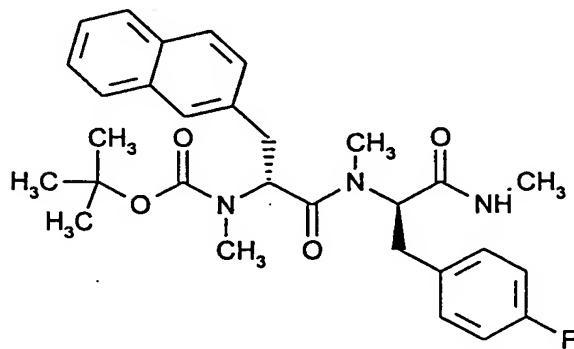
5 min at room temperature. Methylene chloride (30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen carbonate (solid), were added to the reaction mixture, until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.62 g of (2R)-3-(4-fluorophenyl)-N-methyl-2-methylaminopropionamide.

10

¹H-NMR (CDCl₃) δ : 1.31 (s, 1H); 2.29 (s, 3H); 2.65-2.73 (m, 1H); 2.82 (d, 3H); 3.12-3.20 (m, 2H); 6.96-7.02 (m, 2H); 7.11 (s, 1H); 7.14-7.20 (m, 2H).

((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-

15 naphthyl)-ethyl)methylcarbamic acid tert-butylester:



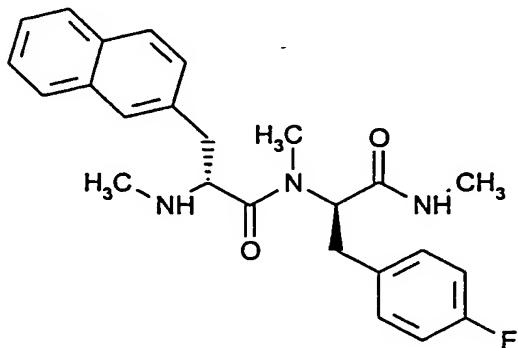
20 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (1.0 g; 3.1 mmol) was dissolved in methylene chloride (20 mL). 1-Hydroxy-7-azabenzotriazole (0.43 g; 3.1 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide

hydrochloride (0.63 g; 3.3 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

(2R)-3-(4-Fluorophenyl)-N-methyl-2-(methylamino)propionamide (0.6 g; 2.9 mmol) and diisopropylethylamine (0.54 mL; 3.1 mmol) was added and the reaction mixture 5 was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was added and the reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was 10 chromatographed on silica (4.0 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.07 g of ((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.34 (s, 9H); 2.23 (d, 3H); 15 2.76 (s, 3H); 2.87 (s, 3H); 5.70 (dd, 1H); 5.95 (dd, 1H).

(2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)-N-methyl-2-methyl-amino-3-(2-naphthyl)propionamide:



20

((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamic acid tert-butylester. (1.0 g; 1.92 mmol) was dissolved in methylene chloride (5 mL). Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 15 min at room temperature. Methylene chloride 25 (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH

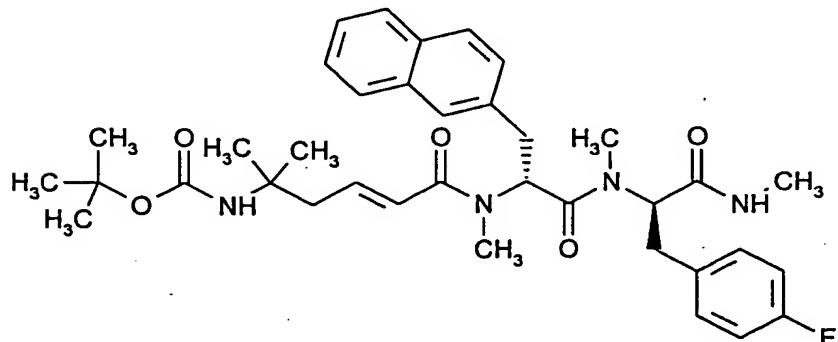
9; 25 mL) and sodium hydrogen carbonate (solid) was added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.75 g of (2R)-N-((1R)-2-(4-fluorophenyl)-1-methylcarbamoylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

5

¹H-NMR (CDCl₃) δ : 1.81 (s, 3H); 2.07 (d, 3H); 2.54 (s, 3H); 2.68-2.77 (m, 1H); 2.88-2.97 (m, 1H); 3.18 (dd, 1H); 3.27 (dd, 1H); 3.8 (dd, 1H); 4.95 (s, 1H); 5.43 (dd, 1H); 6.72 (t, 1H); 6.90 (t, 2H); 7.12 (dd, 2H); 7.32 (d, 1H); 7.42-7.50 (m, 2H); 7.62 (s, 1H); 7.70-7.83 (m, 2H).

10

(4(((1R)-1(((1R)-2(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:



15

(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.22 g; 0.89 mmol, prepared as in example 1) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-

20 ethylcarbodiimide hydrochloride (0.2 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

(2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture was stirred for 12 hours 25 at room temperature.

Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.34 g of (4-(((1R)-1-(((1R)-2-(4-fluorophenyl)-1-methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)-ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.

10 $^1\text{H-NMR}$ (CDCl_3) (selected peaks for major rotamer) d : 0.85 (s, 3H); 0.87 (s, 3H); 1.42 (s, 9H); 2.12 (d, 3H); 2.72 (s, 3H); 2.96 (s, 3H); 5.75 (dd, 1H); 5.92 (dd, 1H); 6.12 (dd, 1H).

15 (4-(((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-methylcarbamoyl-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester (0.33 g; 0.51 mmol) was dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.18 g of the title compound.

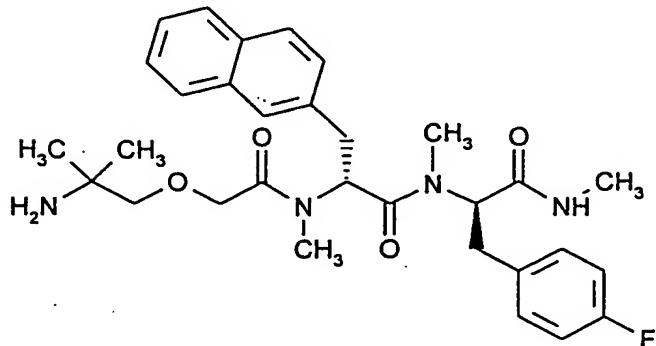
20 $^1\text{H-NMR}$ (CDCl_3) (selected peaks for major rotamer) d : 1.15 (s, 6H); 2.14 (d, 3H); 2.73 (s, 3H); 3.09 (s, 3H); 5.23 (dd, 1H); 5.90 (dd, 1H); 6.12 (dd, 1H).

PDMS: m/z 547.4 (M+H)⁺

HPLC: R_t = 32.05 min (Method A1)

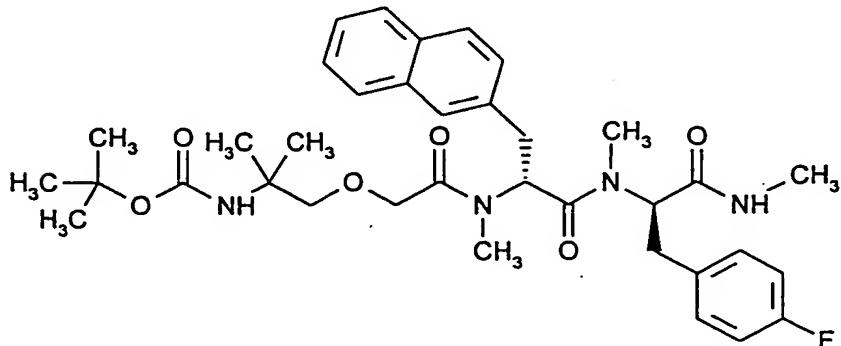
Example 14

(2R)-2-(((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:



(2-(((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-methyl-carbamoylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid

10 tert-butylester:



(2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.22 g; 0.89 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.20 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture

was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.53 g of (2-(((1R)-1-(((1R)-2-(4-fluorophenyl)-1-methylcarbamoyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamoyl)-methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester.

10 $^1\text{H-NMR}$ (CDCl_3) (selected peaks for major rotamer) d : 1.20 (s, 3H); 1.25 (s, 3H); 1.44 (s, 9H); 2.18 (d, 2H); 2.59 (s, 3H); 2.74 (s, 3H); 2.77 (d, 3H); 4.02 (s), 2H); 5.25 (dd, 1H); 5.82 (dd, 1H).

(2-(((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)-methylcarbamoyl)-methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester (0.53 g; 0.81 mmol) was dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.26 g of the title compound.

$^1\text{H-NMR}$ (CDCl_3) (selected peaks for major rotamer) d 0.99 (s, 3H); 1.09 (s, 3H); 2.25 (d, 3H); 2.28 (s, 3H); 2.95 (s, 3H); 3.90 (s, 2H); 5.31 (dd, 1H); 5.83 (dd, 1H).

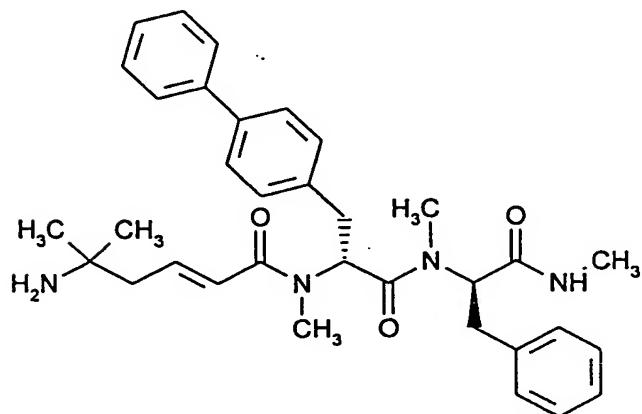
PDMS: m/z 550.6 ($\text{M}+\text{H})^+$

HPLC: $r_t = 31.83$ min (A1)

Example 15

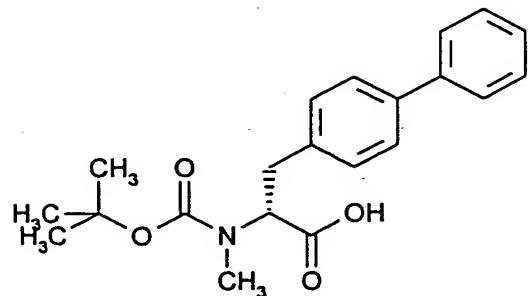
(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-2-(biphenyl-4-yl)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)methylamide:

5



(2R)-3-(1,1'-Biphenyl-4-yl)-2-(N-tert-butoxycarbonyl-N-methylamino)propionic acid:

10



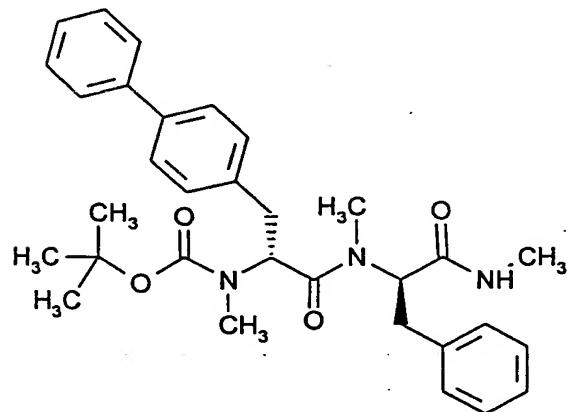
3-(1,1'-Biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionic acid (5.0 g; 14.66 mmol) was dissolved in dry tetrahydrofuran (45 mL). Iodomethane (7.3 mL; 117.3 mmol) was added and the reaction mixture was cooled to 0° C. Sodium hydride (1.75 g; 15 44.0 mmol) was added and the reaction mixture was stirred for 5 days at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise. The solvent was removed in vacuo and the residue was dissolved in an aqueous solution of sodium hydrogen carbonate (saturated; 50 mL) and washed with diethyl ether (30 mL). The aqueous phase was acidified to pH 3 using citric

acid (5 %) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with an aqueous solution of sodium thiosulfate (5 %; 75 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 3.85 g of (2R)-3-(1,1'-biphenyl-4-yl)-2-(N-tert-butoxycarbonyl-N-methylamino)propionic acid.

5

¹H NMR (200 MHz, CDCl₃) δ (mixture of rotamers) 1.47 (s, 4.5H), 1.49 (s, 4.5H), 2.54 (s, 1.5H), 2.56 (s, 1.5H), 3.00-3.40 (bm, 1H), 3.45-3.91 (bm, 1H), 4.53-4.55 (m, 0.5H), 4.55-4.58 (m, 0.5H), 7.3-7.6 (m, 9H).

10 ((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)ethyl)methylcarbamic acid tert-butylester:



(2R)-3-(1,1'-Biphenyl-4-yl)-2-(N-tert-butoxycarbonyl-N-methylamino)propionic acid

15 (1.50 g; 4.23 mmol) was dissolved in methylene chloride (20 mL). 1-Hydroxy-7-azabenzotriazole (0.57 g; 4.23 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.89 g; 4.65 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

N-Methyl-2-methylamino-3-phenylpropionamide (0.81 g; 4.23 mmol) and

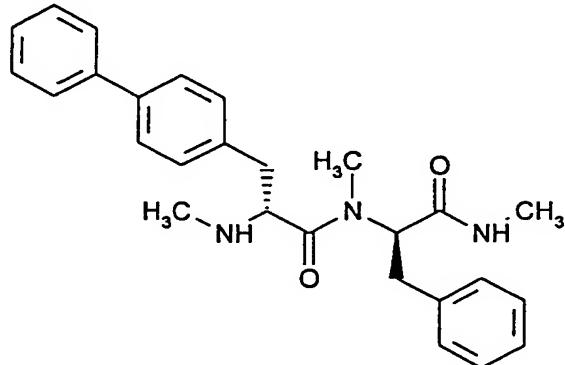
20 diisopropylethylamine (0.73 mL; 4.23 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate (sat; 50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and water (50 mL) and dried (magnesium sulfate).

The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 25 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.02 g of ((1R)-2-(1,1'-biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methylcarbamic acid tert-butyl ester.

5

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.15 (s, 6H); 1.31 and 1.34 (two s; 9H); 2.24 (d, 3H); 2.80 (s, 3H); 2.98 (s, 3H); 4.98 (m, 1H); 5.38 (m, 1H).

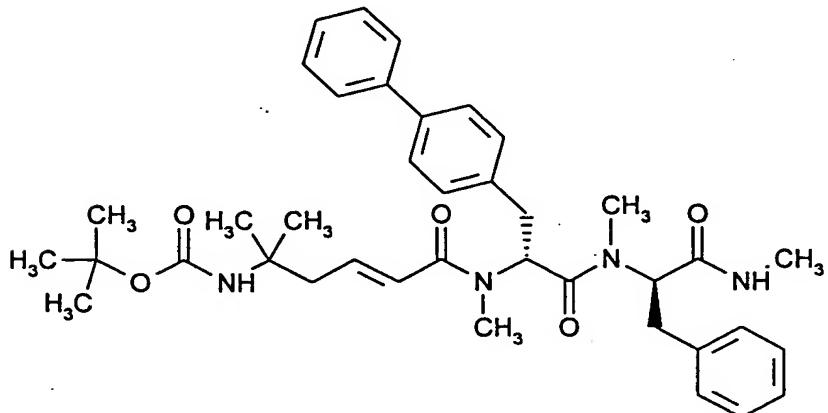
3-(1,1'-Biphenyl-4-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide:



((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)ethyl)methyl-carbamic acid tert-butylester (1.0 g; 1.8 mmol) was dissolved in methylene chloride (4 mL). Trifluoroacetic acid (4 mL) was added and the reaction mixture was stirred for 15 min at room temperature. Methylene chloride (40 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 40 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and the solvent was removed in vacuo to afford 0.76 g of (2R)-3-(1,1'-biphenyl-4-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.71 (s, 3H); 2.58 (s, 3H); 2.69 (d, 3H); 5.52 (dd, 2H).

((3E)-4-(((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.24 g; 0.98 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.2 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-3-(1,1'-Biphenyl-4-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 20 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.46 g of ((3E)-4-(((1R)-2-(1,1'-biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)-carbamic acid tert-butylester.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.22 (s, 3H); 1.23 (s, 3H);

1.42 (s, 9H); 2.75 (d, 3H); 2.82 (s, 3H); 2.98 (s, 3H); 5.54 (dd, 1H); 5.82 (dd, 1H);
6.12 (d, J=17Hz, 1H).

((3E)-4-(((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester (0.45 g; 0.69 mmol) was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (10 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.22 g of the title compound.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.18 (s, 6H); 2.75 (d, 3H);
2.78 (s, 3H); 2.97 (s, 3H); 5.45 (dd, 1H); 5.75 (dd, 1H); 6.08 (d, J=17Hz, 1H).

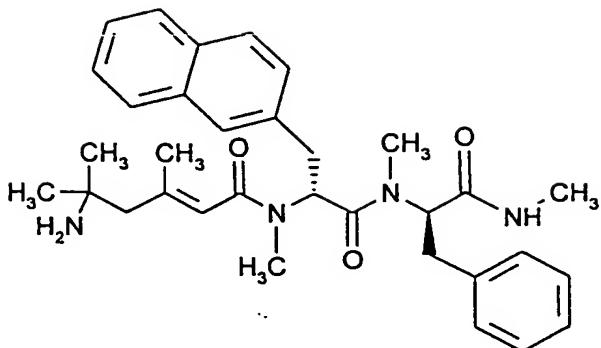
ESMS: m/z 555.8 (M+H)⁺

HPLC: R_t = 34.45 min (Method A1).

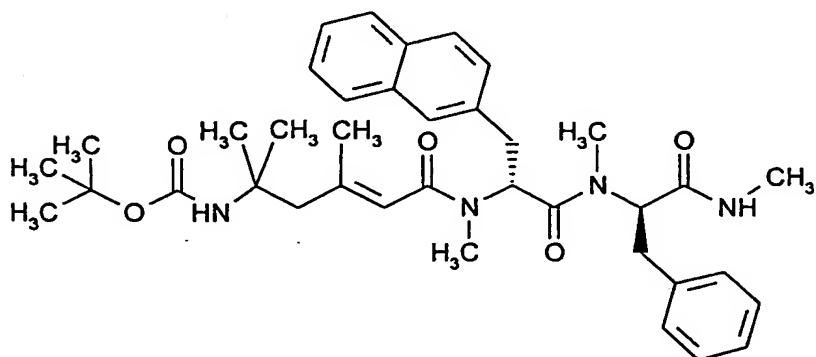
20

Example 16

(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



5 ((3E)-1,1,3-trimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-methyl carbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid
tert butylester:



10 (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid (0.30 g ; 1.17 mmol.) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazol (0.16 g ; 1.17 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g; 1.28 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

15 N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (0.47 g; 1.67 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.20 mL; 1.66 mmol) was added and the reaction was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added and the reaction was washed with water (10 mL) , an aqueous

solution of sodium hydrogen sulfate (10% ; 10 mL) and an aqueous solution of sodium hydrogen carbonate (pH 8 ; 10 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.37 g of
 5 ((3E)-1,1,3-trimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester.

10 ¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.16 (s, 3H); 1.17 (s; 3H); 1.42 (s, 9H); 1.68 (s, 3H); 2.75 (d, 3H); 2.76 (s, 3H); 2.95 (s, 3H); 5.21 (dd, 1H); 5.51 (s, 1H); 5.59 (dd, 1H).

15 ((3E)-1,1,3-Trimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid
 20 tert butylester (0.37 g ; 0.56 mmol) was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (2 mL), water (5mL) and sodium hydrogen carbonate (solid) were added to the reaction until pH = 9. The aqueous phase was extracted with methylene chloride (3 x 10 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.17 g of the title compound.

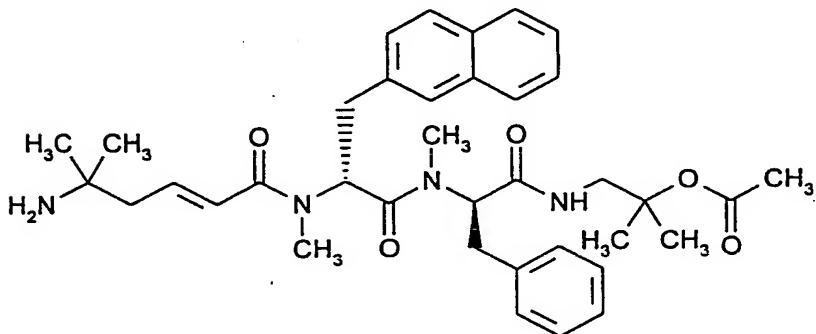
25 ¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.18 (s, 3H); 1.19 (s, 3H); 1.67 (s, 3H); 2.75 (d, 3H); 2.76 (s, 3H); 2.95 (s, 3H); 5.52 (dd, 1H); 5.62 (s, 1H); 5.86 (dd, 1H).

HPLC : R_t = 31.78 min (Method A1)

30 PDMS : m/z 542.8 (M+H)⁺

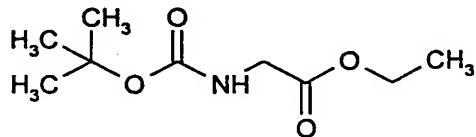
Example 17

5 2-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:



10

Ethyl 2-(tert-butoxycarbonylamino)acetate



15

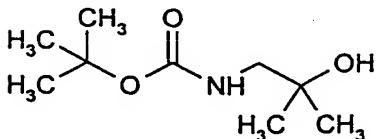
(tert-Butoxycarbonylamino)acetic acid (4.00 g, 22.8 mmol) was dissolved in dichloromethane (8 ml). Ethanol (1.60 ml, 27.40 mmol) and 4-
20 dimethylaminopyridine (0.31 g, 25.1 mmol) were added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (4.81 g, 25.11 mmol) was added. The solution was stirred for 16 h, while warming up to room temperature. It was diluted with ethyl acetate (150 ml) and 10% aqueous sodium hydrogen sulfate solution (100 ml). The phases were separated. The aqueous

phase was extracted with ethyl acetate (4×50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (150 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (100 g), using ethyl acetate/heptane (1:4) as eluent, to give 4.25 g of ethyl 2-(tert-butoxycarbonylamino)acetate.

¹H-NMR (CDCl₃): d 1.30 (t, 3 H); 1.47 (s, 9 H); 3.90 (d, 2 H); 4.21 (q, 2 H); 5.06 (br, 1 H).

10

2-Hydroxy-2-methylpropylcarbamic acid tert-butyl ester



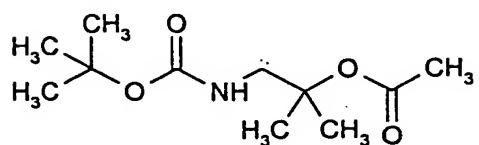
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Ethyl 2-(tert-butoxycarbonylamino)acetate (4.17 g, 20.52 mmol) was dissolved in tetrahydrofuran (60 ml). The solution was cooled to -78 °C. A 22% solution of methyl magnesium chloride in toluene/tetrahydrofuran (purchased from Chemmetallgesellschaft, 27.1 ml, 67.72 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h at -78 °C and then warmed to room temperature. A 10% aqueous solution of ammonium chloride (200 ml) was added dropwise. The phases were separated. The aqueous phase was extracted with ethyl acetate (3×100 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (110 g), using ethyl acetate/heptane (1:1) as eluent, to give 1.31 g of 2-hydroxy-2-methylpropylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): d 1.21 (s, 6 H); 1.45 (s, 9 H); 1.34 (d, 2 H); 5.00 (br, 1 H).

2-(tert-Butoxycarbonylamino)-1,1-dimethylethyl acetate

5



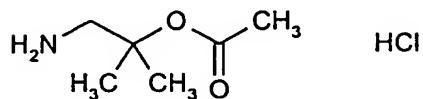
2-Hydroxy-2-methylpropylcarbamic acid tert-butylester (510 mg, 2.69 mmol) was dissolved in dichloromethane (7 ml). The solution was cooled to 0 °C.

10 Ethyldiisopropylamine (0.70 ml, 4.04 mmol), 4-dimethylaminopyridine (33 mg, 0.27 mmol), and acetic acid anhydride (0.33 ml, 3.50 mmol) were added successively. The reaction mixture was stirred for 16 h, while slowly warming up to room temperature. It was diluted with ethyl acetate (30 ml) and extracted with 1N hydrochloric acid (30 ml). The aqueous phase was extracted with ethyl acetate (2 x 15 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (50 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (100 g), using ethyl acetate/heptane (1:2) as eluent, to give 550 mg of 2-(tert-butoxycarbonylamino)-1,1-dimethylethyl acetate.

20

¹H-NMR (CDCl₃): d 1.45 (s, 9 H); 1.46 (s, 6 H); 2.00 (s, 3 H); 3.35 (d, 2 H); 4.96 (br, 1 H).

25 2-Amino-1,1-dimethylethyl acetate hydrochloride



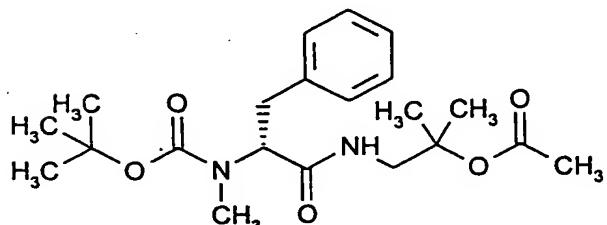
2-(tert-Butoxycarbonylamino)-1,1-dimethylethyl acetate (508 mg, 2.2 mmol) was dissolved in ethyl acetate (6 ml). 3 M hydrogen chloride in ethyl acetate (4 ml, 12 mmol) was added. The reaction mixture was stirred for 20 h at room temperature.

5 The precipitation was filtered off and washed with diethyl ether (50 ml). It was dried in vacuo to give 246 mg of 2-amino-1,1-dimethylethyl acetate hydrochloride.

¹H-NMR (DMSO d₆): δ 1.45 (s, 6 H); 2.00 (s, 3 H); 3.09 (s, 2 H); 8.25 (br, 3 H).

10

2-((2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate



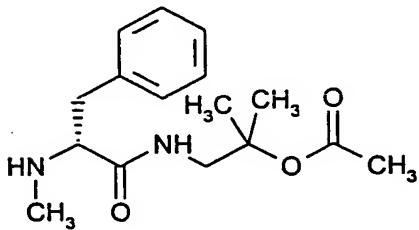
15

(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-phenylpropionic acid (391 mg, 1.4 mmol) was dissolved in N,N-dimethylformamide (6 ml). 1-Hydroxybenzotriazole hydrate (189 mg, 1.4 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride were added. The reaction mixture was stirred for 10 min at room temperature. 2-Amino-1,1-dimethylethyl acetate hydrochloride (237 mg, 1.4 mmol) was added as a solid. Ethyldiisopropylamine (0.53 ml, 3.1 mmol) was added. The reaction mixture was stirred for 20 h at room temperature. It was diluted with ethyl acetate (200 ml) and washed with 1N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was

purified by flash chromatography on silica (80 g), using ethyl acetate/heptane (1:1) as eluent, to give 442 mg of 2-((2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate.

5 ¹H-NMR (CDCl₃): d 1.30 and 1.35 (both s, together 6 H); 1.41 (s, 9 H); 1.98 (s, 3 H); 2.70 - 3.05 (m, 4 H); 3.30 - 3.65 (m, 3 H); 4.75 - 4.95 (m, 1 H); 6.65 (br, 1 H); 7.15 - 7.35 (m, 5 H).

10 1,1-Dimethyl-2-((2R)-2-methylamino-3-phenylpropionylamino)-ethyl acetate:

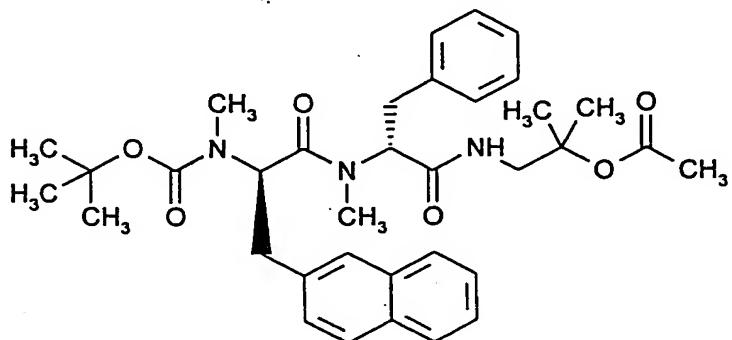


15 2-((2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate (426 mg, 1.1 mmol) was dissolved in dichloromethane (2 ml) and cooled to 0 °C. Trifluoroacetic acid (2 ml) was added and the reaction mixture was stirred for 15 min at 0°C. The solvent was removed in vacuo at 20°C. The residue was dissolved in dichloromethane (50 ml) and the solvent was removed in
20 vacuo. This latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (45 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 312 mg of 1,1-dimethyl-2-((2R)-2-methylamino-3-phenylpropionylamino)ethyl acetate.

25

¹H-NMR (CDCl₃): d 1.43 (s, 6 H); 2.00 (s, 3 H); 2.30 (s, 3 H); 2.67 (dd, 1 H); 3.24 (m, 2 H); 3.53 (ABX, 2 H); 7.15 - 7.45 (m, 5 H); 7.61 (br, 1 H).

2-((2R)-2-(N-((2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-naphthyl)-
5 propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:



(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (373 mg, 1.13 mmol) was dissolved in N,N-dimethylformamide (2 ml) and

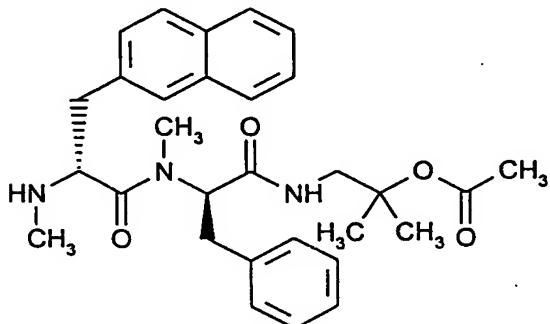
10 dichloromethane (2 ml). 1-Hydroxy-7-azabenzotriazole (153 mg, 1.13 mmol) was added. The solution was cooled to 0°C. N-(3-Dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (217 mg, 1.13 mmol) was added. The reaction mixture was stirred for 10 min at 0 °C. 1,1-Dimethyl-2-((2R)-2-methylamino-3-phenylpropionylamino)-ethyl acetate (301 mg, 1.03 mmol) was dissolved in

15 dichloromethane (2 ml) and added. Ethyldiisopropylamine (0.18 ml, 1.03 mmol) was added. The reaction mixture was stirred for 20 h, while it was warming up to room temperature. It was diluted with ethyl acetate (100 ml) and washed with 1 N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with saturated sodium hydrogen

20 carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (85 g), using ethyl acetate/heptane (1:1) as eluent, to give 547 mg of 2-((2R)-2-(N-((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate.

¹H-NMR (CDCl₃, selected values): d 0.98 and 1.23 (both s, together 9 H); 1.95 and 2.03 (both s, together 3 H); 2.18 and 2.25 (both s, together 3 H); 5.05 and 5.35 - 5.55 (both m, together 2 H).

5 1,1-Dimethyl-2-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropionylamino)ethyl acetate:

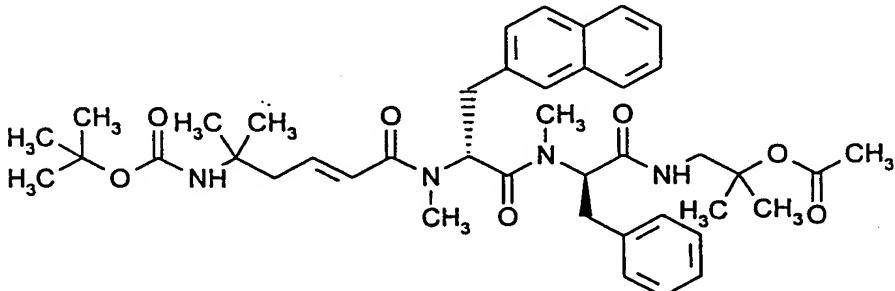


10 2-((2R)-2-(N-((2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-naphthyl)-propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate (511 mg, 0.85 mmol) was dissolved in dichloromethane (2 ml) and cooled to 0 °C. Trifluoroacetic acid (2 ml) was added, and the solution was stirred for 15 min at 0°C. The solvents were removed in vacuo without warming. The residue was dissolved in dichloromethane (50 ml), and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatogrpahy on silica (30 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 160 mg of 1,1-dimethyl-2-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenyl-propionylamino)ethyl acetate.

20

¹H-NMR (CDCl₃, selected values): d 0.82 and 0.90 (s and m, together 6 H); 1.86 and 1.91 (both s, together 3 H); 2.01 and 2.35 (both s, together 3 H); 2.75 and 2.95 (both s, together 3 H); 4.60 and 5.50 (both dd, together 1 H).

2-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:



(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (81 mg, 0.33 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). 1-Hydroxy-7-azabenzotriazole (45 mg, 0.33 mmol) was added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (69 mg, 0.36 mmol) was added. A solution of 1,1-dimethyl-2-((2R)-2-(N-methyl-N-((2R)-2-methylamino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionylamino)ethyl acetate (152 mg, 0.30 mmol) in dichloromethane (2 ml) and ethyldiisopropylamine (0.05 ml, 0.30 mmol) were added successively. The solution was stirred for 16 h, while warming up to room temperature. It was diluted with ethyl acetate (150 ml), washed with 1 N hydrochloric acid (100 ml) and saturated sodium hydrogen carbonate solution, and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (40 g), using ethyl acetate/heptane (first 1:1 (250 ml), then 2:1) to give 221 mg of 2-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate.

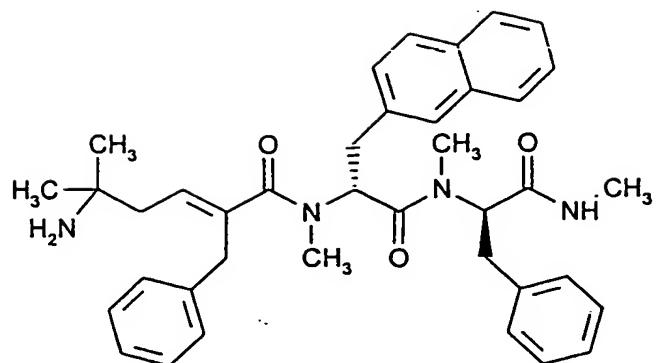
¹H-NMR (CDCl₃, selected values): δ 5.25, 5.45, 5.60, and 5.90 (all dd, together 2 H); 5.92 - 6.07 (m, 1 H); 6.60 - 6.85 (m, 1 H).

2-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate (199 mg, 0.27 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (2 ml) was added. The solution was stirred for 15 min at 0 °C. The solvent was removed in vacuo at 20 °C. The residue was dissolved in dichloromethane (50 ml) and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (25 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 75 mg of the title compound.

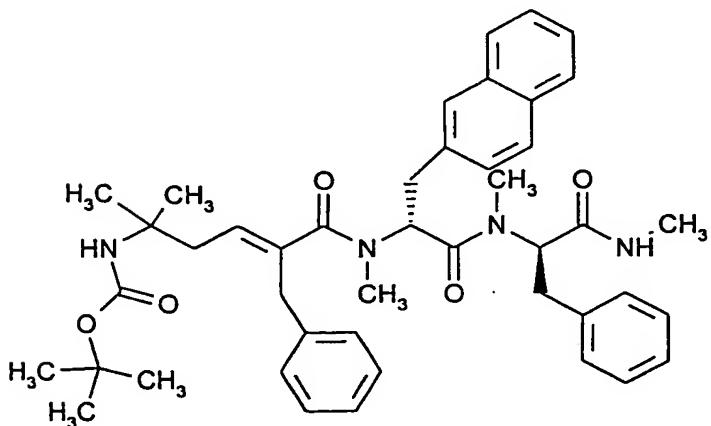
¹H-NMR (CDCl₃, selected values): δ 0.95, 0.96, 0.98, 0.99, 1.16, 1.20, 1.35, and 1.40 (all s, together 12 H); 1.90 and 1.95 (both s, together 3 H); 2.83 and 2.84 (both s, together 3 H); 2.98 and 3.03 (both s, together 3 H); 5.25, 5.45, 5.57, and 5.90 (all dd, together 2 H); 6.95 - 6.10 (m, 1 H); 6.65 - 6.90 (m, 1 H).

HPLC: (A1) R_t = 36.15 min.
MS: 630±1 [M+1]⁺

Example 18
25 (2E)-5-Amino-2-benzyl-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



5 (2E)-2-Benzyl-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid methyl-(1-methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl amide:



10 (2E)-2-Benzyl-5-tert-butoxycarbonylamino-5-methylhex-2-enoic acid (0.125 g; 0.38 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.05 g; 0.37 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.08 g; 0.41 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (0.151 g; 0.37 mmol) was dissolved in methylene chloride (5 mL) and added. Diisopropylethylamine (0.064 mL; 0.37 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (5 mL) was added. The reaction mixture was washed with water (10 mL), an aqueous solution of sodium hydrogen sulfate (10%;

10 mL), and an aqueous solution of sodium hydrogen carbonate (pH 8; 10 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2 x 20 cm) using ethylacetat/methylene chloride 1:1 as eluent to afford 0.08 g of (2E)-2-Benzyl-5-(tert-butoxy-carbonylamino)-5-methylhex-
 5 2-enoic acidmethyl-(1-(methyl-(1-methylcarbamoyl-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl amide.

¹H-NMR: (CDCl₃)(selected peaks for major rotamer) d 0.96 (s, 3H); 1.11 (s, 3H); 1.38 (s, 9H); 2.65 (d, 3H); 2.71 (s, 3H); 2.99 (s, 3H); 4.80 (m, 1H); 5.30 (m, 3H);
 10 5.80 (t, 1H).

(2E)-2-Benzyl-5-(tert butoxycarbonylamino)-5-methylhex-2-enoic acid methyl-(1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl amide
 15 (0.10 g ; 0.14 mmol) was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (1 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (3 mL) and sodium hydrogen carbonate (solid) were added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 10 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.09 g of the title compound.

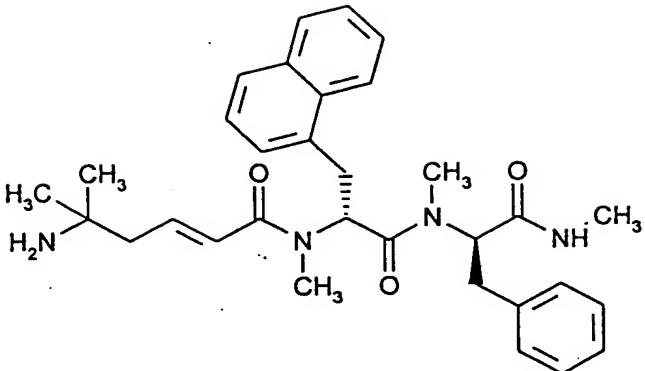
²⁰ ¹H - NMR: (CDCl₃) (selected peaks for major rotamer) d 0.89 (s, 3H); 0.92 (s, 3H); 2.38 (d, 3H); 2.45 (s, 3H); 2.95 (s, 3H); 5.21 (m, 1H); 5.45 (m, 1H).

ESMS : m/z 618.2 (M+H)⁺

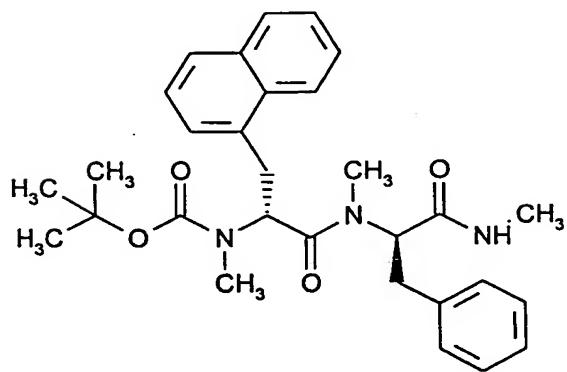
²⁵ HPLC : R_t = 37.53 min (Method A1)

Example 19

³⁰ (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(1-naphthyl)ethyl)amide:



5 Methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert-butylester:



10 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-(1-naphthyl)- propionic acid (2.00 g ; 6.07 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.83 g ; 6.07 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.28 g; 6.68 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-15 3-phenyl-propionamide (1.17 g ; 6.07 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (1.04 mL; 6.07 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (20 mL) was added. The reaction mixture was washed with water (20 mL), an

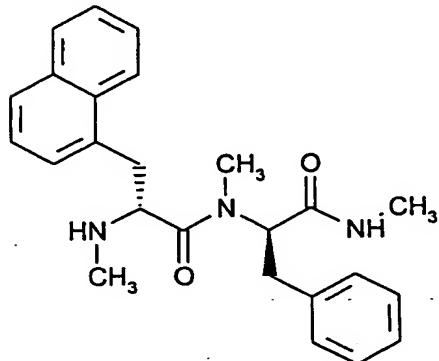
aqueous solution of sodium hydrogen sulfate (10 %; 20 mL), and an aqueous solution of sodium hydrogen carbonate (saturated 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/methylene chloride 1:1 as eluent to afford

5 0.77 g of methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert-butylester.

¹H-NMR : (CDCl₃) (selected peaks for major rotamer) d 1.39 (s, 9H); 2.30 (s, 3H); 2.75 (s, 3H); 3.68 (dd, 1H); 5.35 (dd, 1H).

10

(2R)-N-Methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide:



15

Methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert butyl ester (0.77 g; 1.52 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (4 mL) was added. The reaction

20 mixture was stirred for 30 min at room temperature. Water (5 mL) and methylene chloride (5 mL) were added. An aqueous solution of sodium hydrogen carbonate was added until pH 8. The organic phase was extracted with methylene chloride (3 x 10 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.64 g of (2R)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide.

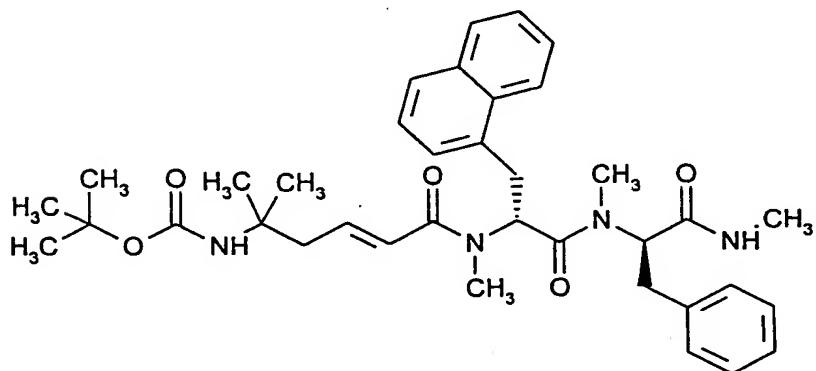
25

¹H-NMR : (CDCl₃)(selected peaks for major rotamer) d 1.69 (s, 3H); 2.05 (s, 3H); 2.57 (d, 3H); 3.91 (dd, 1H); 5.45 (dd, 1H).

5

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester:

10



(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (0.19 g ; 0.80 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.108 g; 0.795 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.87 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide (0.32 g; 0.80 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.14 mL; 0.80 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (5 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethylacetat/methylene chloride 1:1 as

25

eluent to afford 0.26 g of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester.

5 ¹H-NMR : (CDCl₃)(selected peaks for major rotamer) d 1.31 (s, 3H); 1.32 (s, 3H); 1.48 (s, 9H); 2.45 (d, 3H); 2.65 (s, 3H); 2.92 (s, 3H); 5.22 (dd, 1H); 6.03 (dd, 1H); 6.14 (d, 1H).

10 ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester (0.25 g; 0.40 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (5 mL) and solid sodium hydrogen carbonate 15 were added until pH 8. The reaction mixture was washed with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo to afford 0.21 g of the title compound.

19 ¹H-NMR : (CDCl₃) (selected peaks for major rotamer) d 1.22 (s, 3H); 1.23 (s, 3H); 2.82 (d, 3H); 2.92 (s, 3H); 3.08 (s, 3H); 5.22 (dd, 1H); 5.92 (dd, 1H); 6.12 (d, 1H).

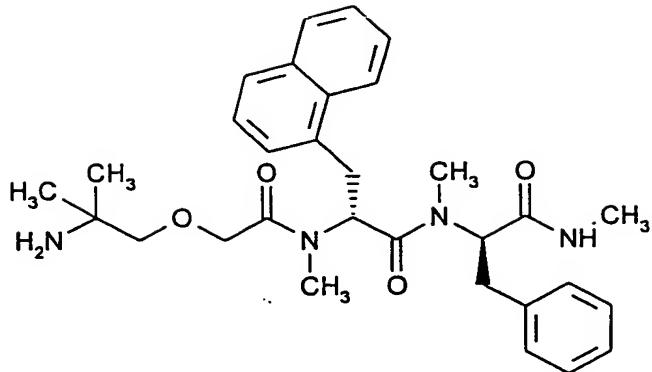
ESMS : m/z 529.2 (M+H)⁺

HPLC : R_t = 30.90 min (Method A1)

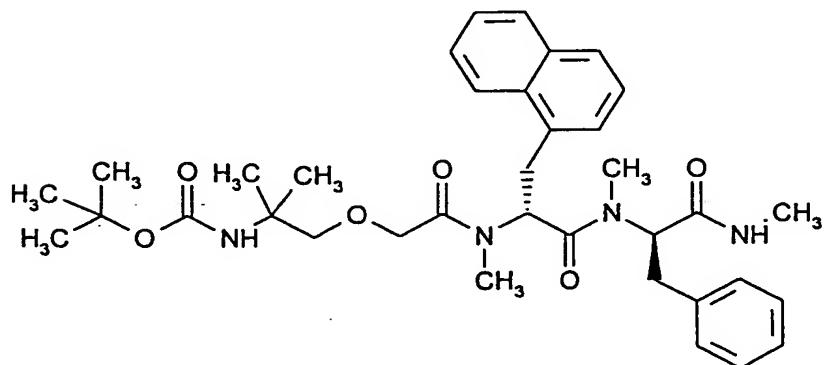
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Example 20

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide:



5 (1,1-Dimethyl-2-((N-methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert butylester:



10 (2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.14 g; 0.54 mmol)(prepared as in example 33) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.07 g; 0.54 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride were added and the reaction mixture was stirred for 15 min at room temperature. (2*R*)-N-Methyl-2-methylamino-N-((1*R*)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl) propionamide (0.21 ; 0.54 mmol) was dissolved in methylene chloride (10 mL) and added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of

sodium hydrogen sulfate (10%; 20 mL) and an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2 x 20 cm) using methylene chloride/ethyl acetate (1:1) as eluent to afford 0.27 g of (1,1-dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.39 (s, 3H); 1.40 (s, 3H); 1.45 (s, 9H); 2.52 (s, 3H); 2.71 (d, 3H); 2.98 (s, 3H); 5.27 (dd, 1H); 5.95 (dd, 1H).

(1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butylester (0.26 g; 0.41 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (5 mL), an aqueous solution of sodium hydrogen carbonate (saturated) and sodium hydrogen carbonate (solid) were added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 15 mL) and the combined organic layers were dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.25 g of the title compound.

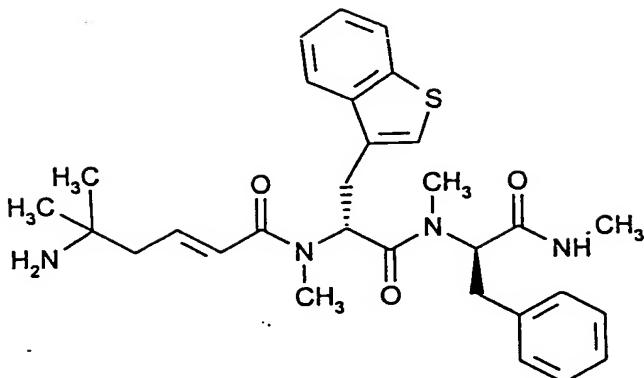
¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.18 (s, 3H); 1.23 (s, 3H); 2.48 (s, 3H); 2.53 (s, 3H); 2.99 (s, 3H); 4.54 (dd, 1H); 5.25 (dd, 1H).

ESMS : m/z 533.2 (M+H)⁺

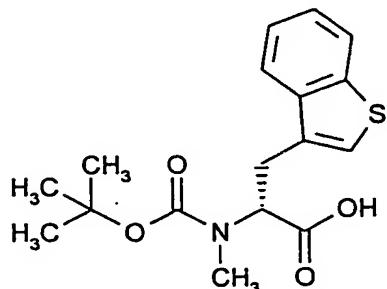
HPLC : R_t = 30.68 min (Method A1)

Example 21

(2E)-5-Amino-5-methylhex-2-enoic acid-((1R)-2-(benzo[b]thiophen-3-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methylamide:



(2R)-3-(Benzo[b]thiophen-3-yl)-2-(tert-butoxycarbonylmethylamino)propionic acid:

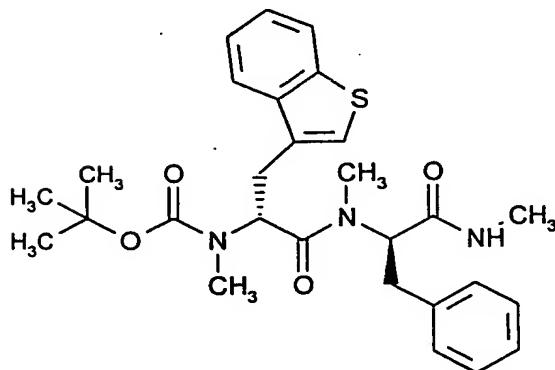


5 (2R)-3-(Benzo[b]thiophen-3-yl)-2-tert-butoxycarbonylamino- propionic acid (2.65 g; 8.25 mmol) was dissolved in dry tetrahydrofuran. Methyl iodide was added and the reaction mixture was cooled to 0 °C. Sodium hydride (60 % in mineral oil, 0.80 g, 24.8 mmol) was added. The reaction mixture was stirred for 48 hours at room
10 temperature. Ethyl acetate (25 mL) and water (10 mL) were added dropwise. The solvent was removed in vacuo and the residue was dissolved in ether (15 mL) and water (15 mL). The organic phase was washed with an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL). To the aqueous phase was added citric acid (5 %) until pH 3 and extracted with ethyl acetate (4 x 20 mL). The combined
15 organic phases were washed with water (2 x 30 mL), an aqueous solution of sodium thiosulfate (5 %; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was dissolved in ether (10 mL). Dicyclohexylamine (5 mL) was added. The precipitated crystals were filtered off, washed with ether (2 x 10 mL) and dissolved in water (30 mL). An aqueous solution
20 of sodium hydrogen sulfate (10 %; 20 mL) and ethyl acetate (40 mL) were added.

The aqueous phase was extracted with ethylacetate (4 x 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 3.75 g of (2R)-3-(benzo[b]thiophen-3-yl)-2-(tert-butoxycarbonyl methylamino)propionic acid.

5 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.45 (s, 9H); 2.81 (s, 3H); 3.21-3.61 (m, 2H); 4.88 (dd, 1H); 7.18 (s, 1H).

((1R)-2-(Benzo[b]thiophen-3-yl)-(methyl-((1R)-1-methylcarbamoyl-2-phenyl-
10 ethyl)carbamoyl)ethyl)methylcarbamic acid tert butylester:



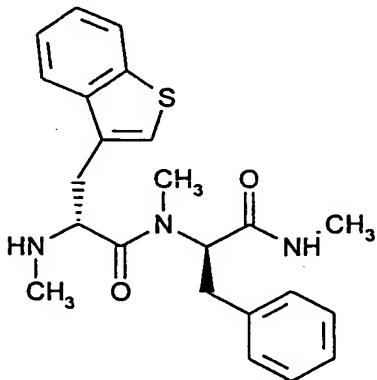
(2R)-3-(Benzo[b]thiophen-3-yl)-2-(tert-butoxycarbonyl- methylamino)propionic acid
15 (2.00 g ; 5.96 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.81 g; 5.96 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.26 g ; 6.56 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-3-phenylpropionamide (1.15 g; 5.96 mmol) was dissolved
20 in methylene chloride (10 mL) and added. Diisopropylethylamine (1.02 mL; 5.96 mmol) were added. The reaction mixture was stirred for 48 hours. Methylene chloride (10 mL) was added. The reaction was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and dried (magnesium sulfate).
25 The solvent was removed in vacuo and the residue was chromatographed on silica

(3 x 30 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.89 g of ((1R)-2-(benzo[b]thiophen-3-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl carbamic acid tert-butylester.

5 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.43 (s, 9H); 2.26 (d, 3H); 2.75 (s, 3H); 2.76 (s, 3H); 4.96 (dd, 1H); 5.05 (dd, 1H).

(2R)-3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide:

10



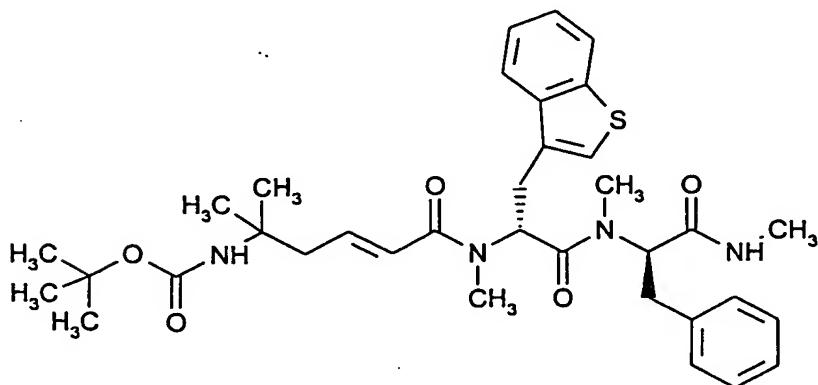
((1R)-2-(Benzo[b]thiophen-3-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl carbamic acid tert-butylester (0.89 g; 1.70 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added.

15 The reaction mixture was stirred for 45 min at room temperature. Water (5 mL) was added. Methylene chloride (5 mL), an aqueous solution of sodium hydrogen carbonate (saturated) and sodium hydrogen carbonate (solid) was added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo
20 to afford 0.66 g of (2R)-3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.71 (s, 3H); 2.38 (s, 3H); 2.62 (d, 3H); 3.82 (dd, 1H); 5.47 (dd, 1H).

((3E)-4-(((1R)-2-(Benzo[b]thiophen-3-yl)-1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:

5



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.19 g; 0.78 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.11 g; 0.78 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (0.16 g; 0.86 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.

3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide (0.32 g; 0.78 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.13 mL; 0.78 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature.

Methylene chloride (10 mL) was added. The reaction was washed with water (20 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 20 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2 x 20 cm) using ethylacetate/methylene chloride (1:1) as eluent to afford 0.26 g of ((3E)-4-(((1R)-2-(benzo[b]thiophen-3-yl)-1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester.

H3C
H3C
H3C
H3C
H3C
H3C
H3C

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 3H); 1.27 (s, 3H); 1.38 (s, 9H); 2.47 (s, 3H); 2.72 (d, 3H); 2.98 (s, 3H); 5.06 (dd, 1H); 5.67 (dd, 1H); 6.08 (d, 1H).

5

((3E)-4-(((1R)-2-(Benzo[b]thiophen-3-yl)-1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at roomtemperature.

10 Water (5 mL) was added. Methylene chloride (8 mL), an aqueous solution of sodium hydrogen carbonate (saturated), sodium hydrogen carbonate (solid) was added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 10 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to give 0.13 g of the title compound.

15

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 6H); 2.47, (s, 3H); 2.75 (d, 3H); 2.96 (s, 3H); 4.98 (dd, 1H); 5.89 (dd, 1H); 6.10 (d, 1H).

PDMS : m/z 535.7 (M+H)⁺

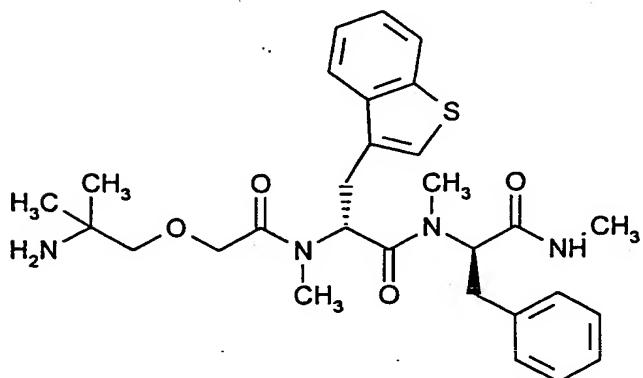
20

HPLC : R_t = 30.87 min (Method A1)

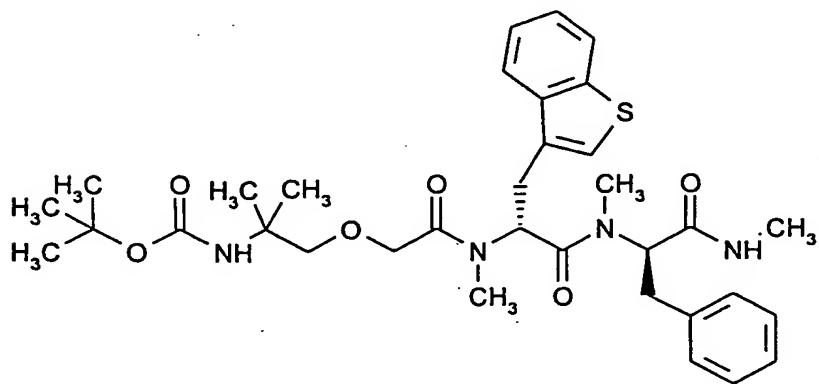
Example 22

(2R)-2-(((2-Amino-2-methylpropoxy)acetyl)methyl- amino)-3-(benzo[b]thiophen-3-yl)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide:

5



(2-(((1R)-2-(Benzo[b]thiophen-3-yl)-((methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl carbamoyl)methoxy)-1,1-dimethylethyl)-carbamic acid tert butyl ester:



15 (2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.193 g ; 0.78 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.11 g; 0.78 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.16 g; 0.86 mmol) were added. The reaction mixture was stirred for 15 min at

room temperature. (2R)-3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide (0.32 g ; 0.78 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.13 mL; 0.78 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added. The reaction was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 20 mL) and an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.44 g of (2-(((1R)-2-(benzo[b]thiophen-3-yl)-1-((methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-ethyl)methyl carbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert butyl ester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 3H); 1.28 (s, 3H); 1.42 (s, 9H); 2.70 (s, 3H); 2.78 (d, 3H); 2.97 (s, 3H); 4.99 (dd, 1H); 5.88 (dd, 1H).

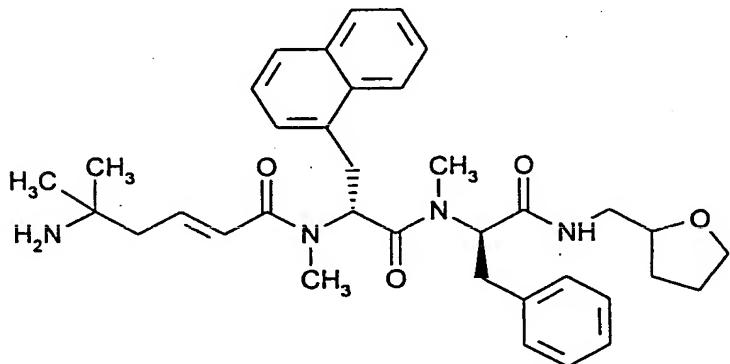
(2-(((1R)-2-(Benzo[b]thiophen-3-yl)-1-((methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl carbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert butyl ester (0.435 g; 0.68 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Water (5 mL) was added. Methylene chloride (8 mL), an aqueous solution of sodium hydrogen carbonate (saturated) and solid sodium hydrogen carbonate was added until pH 8. The aqueous phase was washed with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo to afford 0.36 g of the title compound.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 6H); 2.65 (s, 3H); 2.75 (s, 3H); 2.98 (s, 3H); 4.68 (dd, 1H); 5.79 (dd, 1H).

PDMS : m/z 538.1 (M+H)⁺

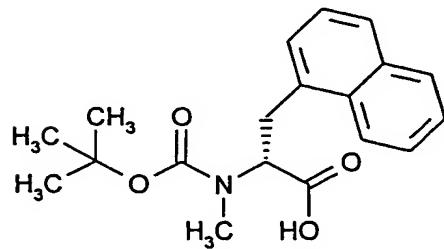
5 Example 23

(2E)-5-Amino-5-methylhex-2-enoic acid methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)-amide:



10

(2R)-2-(tert-Butoxycarbonylmethylamino)-3-(1-naphthyl)-propionic acid:



15

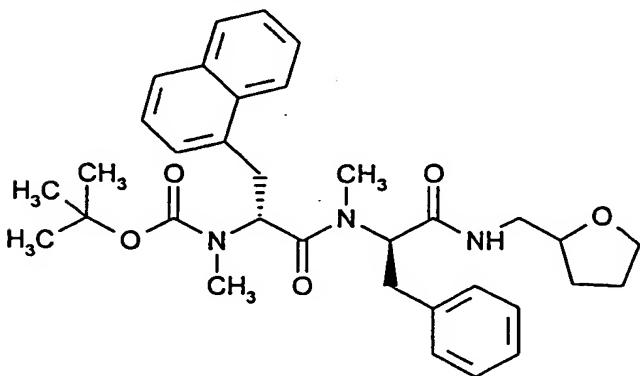
2-tert-Butoxycarbonylamino-3-(1-naphthyl)propionic acid (5.0 g; 0.015 mol) was dissolved in tetrahydrofuran (40 mL). Iodomethane (7.6 mL; 0.12 mol) was added. The reaction mixture was cooled to 0 °C and sodium hydride was added. The reaction mixture was stirred for 48 hours. Ethyl acetate (50 mL) and water (20 mL) were added dropwise. The solvent was removed in vacuo and ether (30 mL) and

water (20 mL) were added. The organic phase was washed with an aqueous solution of sodium hydrogen carbonate (pH 8 ; 30 mL). To the aqueous phases was added citric acid (5%) to pH 3. The aqueous phase was extracted with ethylacetate (3 x 30 mL). The combined organic phases were washed with water (2 x 40 mL), an aqueous solution of sodiumthiosulfate (5 % ; 40 mL) and water (40 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and ether (10 mL) and dicyclohexylamine (8.5 mL) were added. The precipitated crystals were filtered off and dissolved in water (20 mL). Hydrochloric acid was added to pH 2. The reaction mixture was extracted with ethyl acetate (4 x 40 mL), dried (magnesium sulfate) and evaporated in vacuo to afford 3.97 g of (2R)-2-(tert-butoxycarbonyl methylamino)-3-(1-naphthyl)propionic acid.

¹H-NMR : (CDCl₃) d 1.01 (s, 9H); 2.76 (s, 3H); 3.32 (dd, 1H); 3.93 (dd, 1H); 4.95 (dd, 1H); 7.30-8.10 (7 arom. H)

15

Methyl-((1*R*)-1-(methyl-((1*R*)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)-carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert-butylester:



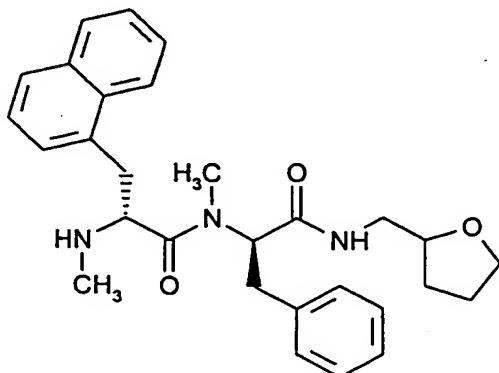
²⁰ (2R)-2-(tert-Butoxycarbonylmethylamino)-3-(1-naphthyl)-propionic acid (0.68 g; 2.06 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazol (0.28 g; 2.06 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.43 g; 2.26 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.

(2R)-2-Methylamino-3-phenyl-N-((2-tetrahydrofuryl)-methyl)propionamide (0.54 g; 2.058 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.35 mL; 2.06 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Methylenec chloride (10 mL) was 5 added. The reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10%; 30 mL), an aqueous solution of sodium hydrogen carbonate (pH 8; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (5 x 50 cm) using ethyl acetate/methylene chloride 1:1 as eluent to afford 1.08 g of methyl-((1R)-1-(methyl-
10 ((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 0.71 (s, 9H); 1.64 (s, 3H); 2.25 (s, 3H); 2.83 (d, 2H); 2.85 (s, 3H); 5.15 (dd, 1H); 5.44 (dd, 1H).

15

(2R)-N-Methyl-2-methylamino-3-(1-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide:



20

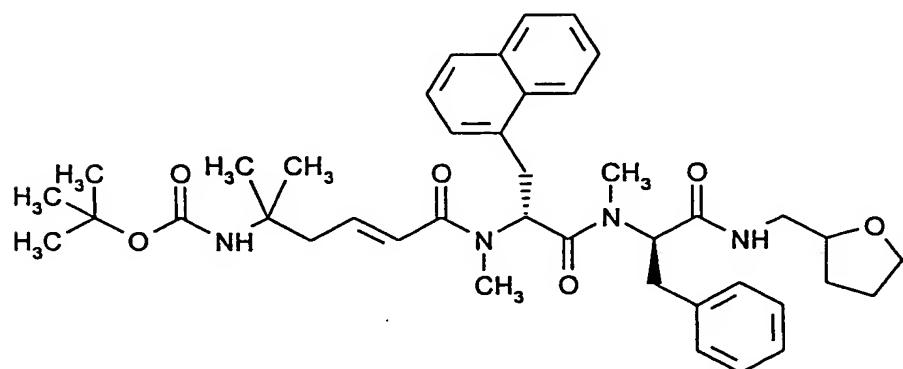
Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert butylester (0.84 g; 1.46 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) 25 was added. The reaction mixture was stirred for 5 min at roomtemperature. Water

(3 mL) and methylene chloride (5 mL) was added. Sodium hydrogen carbonate (solid) was added until pH 8. The reaction mixture was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried (magnesium sulfate) and evaporated in vacuo to afford 0.68 g of (2R)-N-methyl-2-methylamino-3-(1-naphthyl)-N-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl-methyl)-carbamoyl)ethyl)propionamide.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.75 (s, 3H); 2.08 (s, 3H); 2.40 (d, 2H); 2.95 (d, 3H); 4.45 (m, 1H); 5.45-5.50 (m, 2H).

10

((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-carbamoyl)-2(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester:



15

(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (0.344 g; 1.41 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.19 g; 1.41 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.298 g; 1.56 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-3-(1-naphthyl)-N-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide (0.67 g; 1.42 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.242 mL; 1.41 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (20 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (

10 %;30 mL), an aqueous solution of sodium hydrogen carbonate (pH 8 ; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using methylene chloride/ethyl acetate (1:1) as eluent to afford 0.81 g of ((3E)-1,1-dimethyl-4-(methyl-((1R)-1-(methyl-
5 ((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.28 (s, 9H); 1.47 (s, 6H); 2.90 (d, 3H); 6.06 (d, 1H).

10 ((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-carbamoyl)-2(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester (0.80 g; 1.15 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was
15 stirred for 5 min at room temperature. Methylene chloride (5 mL) and sodium hydrogen carbonate were added until pH 8. The reaction mixture was extracted with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo to afford 0.50 g of the title compound.

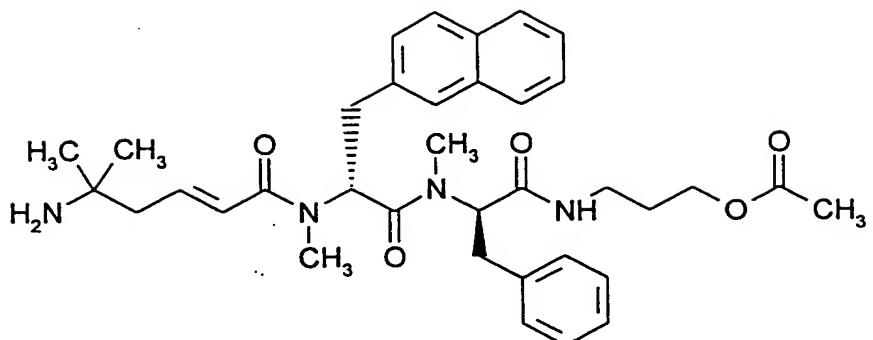
20 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 6H); 2.25 (d, 2H); 2.08 (s, 3H); 2.89 (d, 3H); 3.18 (s, 3H); 5.90 (dd, 1H); 6.65 (d, 1H).

PDMS: m/z 599.8 (M+H)⁺

25 HPLC : R_t = 33.50 (Method A1)

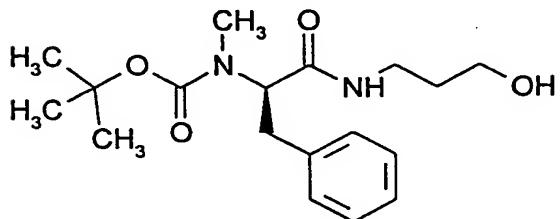
Example 24

30 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



5

N-((1*R*)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester:



10

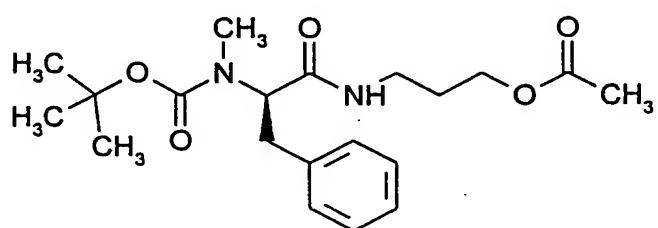
3-Aminopropan-1-ol (0.39 mL, 5.12 mmol) was added at room temperature to a solution of N-tert-butoxycarbonyl-N-methyl-D-phenylalanine (1.30 g, 4.65 mmol) in N,N-dimethylformamide (40 mL). 1-Hydroxybenzotriazole monohydrate (0.63 g, 4.65 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.89 g, 4.65 mmol) were added successively. The reaction mixture was stirred for 22 h at room temperature. It was diluted with 10% sodium hydrogensulfate solution (300 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica (45 g) with dichloromethane/methanol (10:1) to give 1.01 g of N-((1*R*)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

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¹H-NMR (CDCl₃): δ 1.30 and 1.40 (both s, together 9 H); 1.65 and 1.72 (both br, together 2 H); 2.77 (s, 3 H); 2.90 - 3.75 (m, 6 H); 4.75 and 4.86 (both m, together 1 H); 6.50 (m, 1 H); 7.10 - 7.25 (m, 5 H).

5

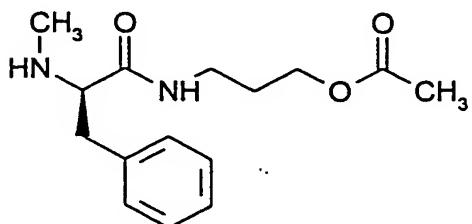
3-((2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-phenylpropionylamino)propyl acetate:



10 A solution of N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester (965 mg, 2.86 mmol) in dichloromethane (10 mL) was cooled to 0°C. 4-(dimethylamino)pyridine (35 mg, 0.29 mmol), triethylamine (0.60 mL, 4.29 mmol), and acetic acid anhydride (0.32 mL, 3.43 mmol) were added. The reaction mixture was stirred for 5 hours, while it was warming slowly to room
15 temperature. The reaction mixture was diluted with dichloromethane (100 mL) and washed with 10% sodium hydrogensulfate solution. The aqueous phase was extracted with dichloromethane (2 x 50 mL). The organic phases were combined and washed with saturated sodium hydrogen carbonate solution. They were dried over magnesium sulfate. The solvent was removed in vacuo, and the crude product
20 was purified by flash chromatography on silica (90 g) with ethyl acetate/dichloromethane (1:3 to 1:1) to give 890 mg of 3-((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropionylamino)propyl acetate.

25 ¹H-NMR (CDCl₃) δ 1.25 and 1.39 (both s, together 9 H); 1.85 (m, 2 H); 2.06 and 2.07 (both s, together 3 H); 2.76 (s, 3 H); 2.95 (m, 1 H); 3.35 (m, 3H); 4.00 - 4.20 (m, 2 H); 4.70 - 4.87 (both m, together 1 H); 6.22 and 6.37 (both br, together 1 H); 7.10 - 7.35 (m, 5 H).

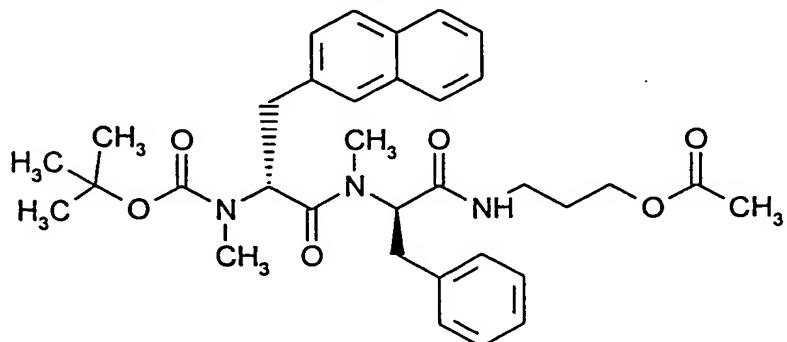
3-((2R)-2-(Methylamino)-3-phenylpropionylamino)propyl acetate:



5 A solution of 3-((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropionylamino)propyl acetate (862 mg, 2.28 mmol) in dichloromethane (3 mL) was cooled to 0°C. Trifluoroacetic acid (3 mL) was added. The solution was stirred for 10 min. The solvents were removed in vacuo without warming. The residue was dissolved in dichloromethane (50 mL) and the solvent was removed in vacuo. The 10 procedure was repeated twice. The crude product was purified by flash chromatography on silica (70 g) with dichloromethane/methanol/25% ammonia in water (100:10:1) to give 602 mg of 3-((2R)-2-(methylamino)-3-phenylpropionylamino)propyl acetate.

15 $^1\text{H-NMR}$ (CDCl_3) δ 1.85 (m, 2 H); 2.07 (s, 3 H); 2.80 (s, 3 H); 2.72 (dd, 1 H); 3.20 (m, 2 H); 3.35 (m, 2 H); 4.10 (t, 1 H); 7.15 - 7.40 (m, 6 H).

3-((2R)-2-(N-((2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:

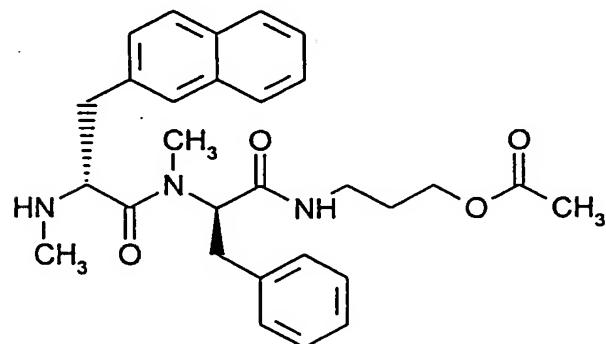


(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)-propionic acid (659 mg, 2.0 mmol) was dissolved in N,N-dimethylformamide (3 mL) and dichloromethane (3 mL). The solution was cooled to 0°C. 1-Hydroxy-7-azabenzotriazole (272 mg, 2.0 mmol) was added. After 10 min N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (460 mg, 2.4 mmol) was added. The reaction mixture was stirred for 10 min. A solution of 3-((2R)-2-(methylamino)-3-phenylpropionylamino)propyl acetate (567 mg, 2.0 mmol) in dichloromethane (4 mL) was added. The solution was stirred for 16 hours, while the temperature rose to room temperature. The reaction mixture was diluted with ethyl acetate (150 mL). It was extracted with 10% sodium hydrogensulfate solution (150 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic phases were combined and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (70 g) with ethyl acetate/heptane (2:1) to give 973 mg of 3-((2R)-2-(N-((2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)-propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate.

¹H-NMR (CDCl₃): δ 4.99, 5.11, 5.18, 5.35, and 5.42 (all dd, together 2 H); 5.75 and 6.15 (both t, together 1 H).

20

3-((2R)-2-(N-((2R)-2-Methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:

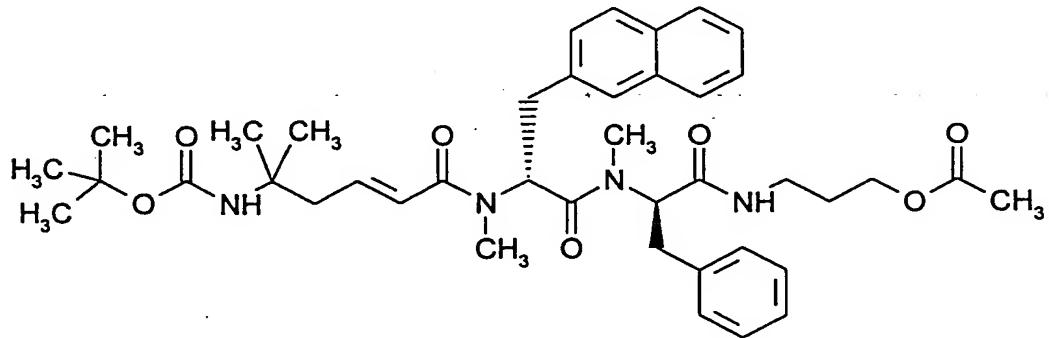


25 At 0°C, trifluoroacetic acid (3 mL) was added to a solution of 3-((2R)-2-(N-((2R)-2-

(N-(tert-butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate (885 mg, 1.50 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 5 min. The solvents were removed in vacuo at 20°C. The residue was dissolved in dichloromethane (40 mL). The procedure was repeated twice. The crude product was purified by flash chromatography on silica (45 g) with dichloromethane/methanol/25% solution of ammonia in water (100:10:1) to give 497 mg of 3-((2R)-2-(N-((2R)-2-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate.

10 $^1\text{H-NMR}$ (DMSO-d₆): δ 1.65 (m, 2 H); 2.01 and 2.02 (both s, together 3 H); 4.67 and 5.35 (both dd, together 1 H).

15 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



20 (2E)-5-tert-Butoxycarbonylamino-5-methylhex-2-enoic acid (277 mg, 1.14 mmol) and 1-hydroxy-7-azabenzotriazole (155 mg, 1.14 mmol) were dissolved in dichloromethane (3 mL) and N,N-dimethylformamide (3 mL). The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (254 mg, 1.32 mmol) was added. The solution was stirred for 10 min at 0°C, before a

solution of 3-((2R)-2-(N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate in dichloromethane (3 mL) was added. The solution was stirred for 18 hours, while it was warming up slowly to room temperature. It was diluted with ethyl acetate (100 mL) and extracted with 5 10% sodium hydrogensulfate solution. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (45 g) with ethyl acetate/heptane (2:1) to give 427 mg of 10 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate.

¹H-NMR (CDCl₃): δ 1.80 (m, 2 H); 4.10 (m, 2 H); 6.05 (m, 1 H); 6.75 (m, 1 H).

15 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate (412 mg, 0.58 mmol) was dissolved in dichloromethane (2 mL). The solution was cooled to 0 °C. Trifluoroacetic acid (2 20 mL) was added. The soltuion was stirred for 8 min at 0 °C, and the solvents were removed in vacuo with a water bath temperature of 20°C. The residue was dissolved in dichloromethane (30 mL) and the solvent was removed in vacuo. This latter procedure was repeated twice. The crude product was purified by flash chromatography on silica (35 g) with dichloromethane/methanol/25% ammonia in 25 water (100:10:1). The product was dissolved in ethyl acetate (3 mL) and 3M hydrogen chloride in ethyl acetate (0.7 mL) was added. The solvent was removed in vacuo and the product was dried over night in vacuo to give 0.21 g of title compound as a hydrochloride.

30 ¹H-NMR (DMSO-d₆) (selected values) δ 1.70 (m, 2H); 4.00 (m, 2H).

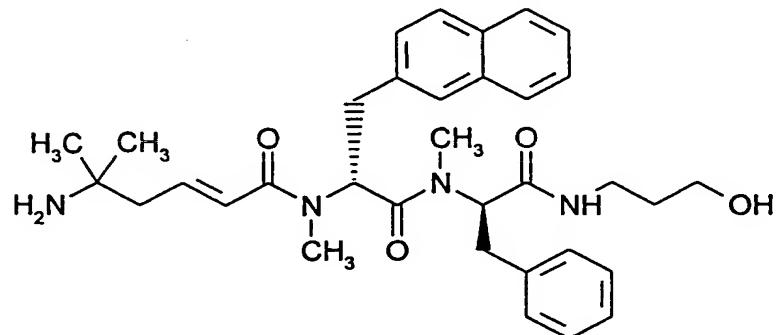
MS: found: 616.3 ± 1 [M+1][†]

HPLC: R_T = 20.47 min (method A1)

5

Example 25

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methyl-
10 amide:



15 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-anphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate hydrochloride (140 mg, 0.21 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of lithium hydroxide (18 mg, 0.74 mmol) in water (1.5 mL) was added. Water was added until a clear solution was obtained. The reaction mixture was stirred for 16 h
20 at room temp. It was diluted with water (30 mL) and extracted with tert-butylmethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed in vacuo. The residue was dissolved in water (15 mL) and acetic acid (0.8 mL) and the resulting solution was lyophilized to give 105 mg of the acetate salt of the title compound.

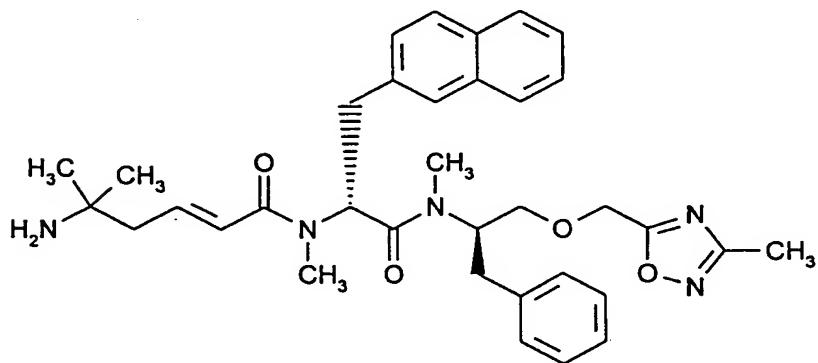
¹H-NMR (DMSO-d₆) (selected peaks): δ 0.95 (s, 6 H); 1.55 (m, 3H); 3.42 (m, 2H).

HPLC: $R_T = 30.97$ min (method A1)

5

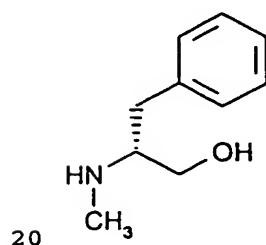
Example 26

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



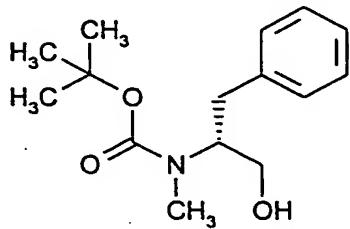
15

(2R)-2-(Methylamino)-3-phenylpropan-1-ol:



(2R)-2-(Methylamino)-3-phenylpropan-1-ol was prepared analogue to M. J. McKennon and A. I. Meyers J. Org. Chem. 1993 (58), 3568 - 3571. m.p. 69 - 69°C (lit: A. I. Meyers, J. Org. Chem. 1993 (58), 3568 - 3571; 71 - 74 °C; A. Karim, A. Mortreux, F. Petit, G. Buono, G. Pfeiffer, C. Siv, J. Organomet. Chem. 1986, 317, 93; 68 °C, for (2S)-2-(methylamino)-3-phenylpropan-1-ol)

N-((1R)-1-Hydroxymethyl-2-phenylethyl)-N-methyl carbamaic acid tert-butylester:

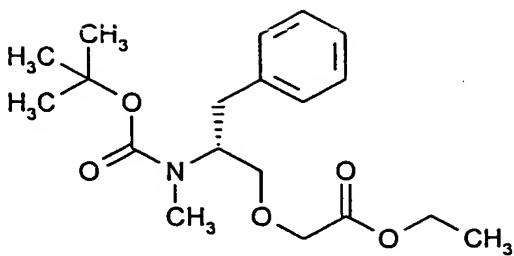


10 (2R)-2-(Methylamino)-3-phenylpropan-1-ol (6.00 g, 36.3 mmol) was dissolved in Tetrahydrofuran (80 mL). 1N sodium hydroxide solution (36.3 mL, 36.3 mmol) was added. A solution of di-tert.-butyl dicarbonate (9.50 g, 43.6 mmol) in tetrahydrofuran (60 mL) was slowly added at room temperature. The solution was stirred 16 h at room temperature. Water (200 mL) and ethyl acetate (200 mL) were added. The 15 phases were separated. The aqueous phase was washed with ethyl acetate (2 x 100 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed in vacuum. The product was purified on silica (170 g) with ethyl acetate/heptane (1:1) to give 7.85 g (81%) of N-((1R)-1-hydroxymethyl-2-phenylethyl)-N-methyl carbamaic acid tert-butylester.

20

1H-NMR (CDCl_3): $\delta = 1.32 - 1.40$ (br, 9H); 2.55 - 2.95 (m, 5 H); 3.65 - 3.67 (br, 2 H); 4.10 - 4.35 (br, 1H); 7.05 - 7.35 (m, 5 H).

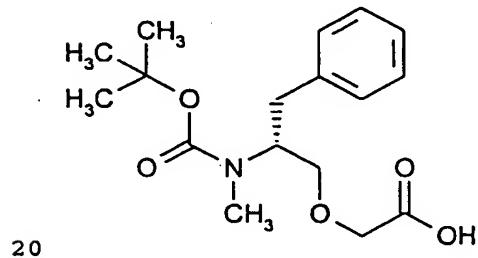
25 ((2R)-2-(tert-Butoxycarbonylmethylamino)-3-phenylpropoxyl)acetic acid ethyl ester:



N-((1R)-1-Hydroxymethyl-2-phenylethyl)-N-methyl carbamaic acid (3.98 g, 15.0 mmol) was dissolved in 1,2-dichloroethane (150 mL). The solution was warmed to 5 75 - 80 °C. Rhodium(II) acetate (0.1 g, 0.4 mmol) was added. During a period of 6 hours a solution of ethyl diazoacetate (2.4 mL, 22.5 mmol) in dichloromethane (100 mL) was added. After 3 h another portion of rhodium(II) acetate (0.1 g, 0.4 mmol) was added. After addition of ethyl diazoacetate, the solution was cooled to room temperature. It was filtered through a plug of celite. The solvent was removed in 10 vacuum. The crude product was chromatographed on silica (100 g) to give 1.53 g of ((2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropoxyl)acetic acid ethyl ester.

1H-NMR (CDCl₃): δ = 1.28 (m, 3 H); 1.39 and 1.48 (both s, together 9H); 2.65 - 2.95 15 (m, 9 H); 3.58 (m, 1 H); 3.67 (br, 1H); 3.98 - 4.27 (m, 4 H); 4.35 - 4.55 (br, 1H); 7.10 - 7.30 (m, 5 H).

((2R)-2-(tert-Butoxycarbonylmethylamino)-3-phenylpropoxy)-acetic acid:

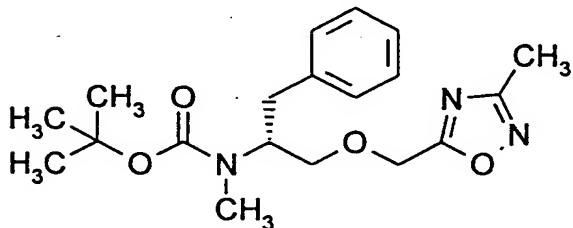


((2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropoxyl)-acetic acid ethyl ester (0.60 g, 1.71 mmol) was dissolved in dioxane (5 mL). A solution of lithium hydroxide

(0.05g, 2.20 mmol) in water (2 mL) was added. The solution was stirred at room temperature for 56 hours. Ethyl acetate (10 mL) and water (2 mL) were added. The phases were separated. The aqueous phase was extracted with ethyl acetate (10 mL). The combined organic layers were extracted with 1N sodium hydroxide solution (20 mL). The combined aqueous phases were acidified with a 1M sodium hydrogensulfate solution (pH 2) and extracted with ethyl acetate (2 x 20 mL). These ethyl acetate layers were combined and dried over magnesium sulfate. The solvent was removed in vacuum to give 0.38 g of crude ((2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropoxy) acetic acid, which was used for the following steps.

¹⁵ ^{1H-NMR (DMSO d₆): d = 1.15 and 1.27 (both s, together 9H); 2.55 - 2.70 (m, 5 H); 3.45 - 3.65 (m, 2 H); 4.00 - 4.10 (m, 2 H); 4.30 - 4.50 (m, 1H); 7.15 - 7.35 (m, 5 H); 13.60 (br, 1H).}

N-Methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl-2-phenylethyl)carbamic acid tert-butylester:



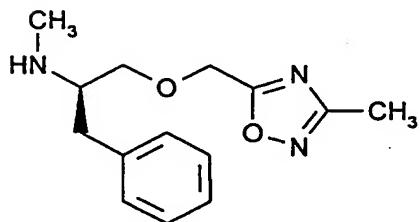
²⁰ At -13 °C, isobutyl chloroformate (0.80 mL, 6.19 mmol) was added slowly to a solution of ((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropoxy)acetic acid (2.0 g, 6.18 mmol) and N-methylmorpholine (0.68 mL, 6.18 mmol) in tetrahydrofuran (25 mL). The solution was stirred for 15 min at this temperature. ²⁵ Acetamidoxim (0.92 g, 12.36 mmol) was added as a solid. Immediately after addition, N-methylmorpholine (0.68 mL, 6.18 mmol) was given to the reaction mixture. It was stirred for 45 min at -13°C, 3.5 h at room temperature and 16 hours at reflux. The reaction mixture was cooled to room temperature and diluted with

ethyl acetate (100 mL). It was extracted with water and 10% sodium hydrogensulfate solution (10 mL/40 mL). The aqueous phase was extracted with ethyl acetate (2x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate.

5 The solvent was removed in vacuo. The crude product was purified on silica (90 g) with ethyl acetate/heptane (1:1) as eluent to give 1.17 g of N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl-2-phenylethyl)carbamcic acid tert-butylester.

10 ¹H-NMR (CDCl₃) δ 1.31 and 1.39 (both s, together 9H); 2.43 (s, 3H); 2.65 - 2.95 (m, 5H); 3.65 (m, 1H); 3.76 (m, 1H); 4.43 and 4.53 (both br, together 1H); 4.70 - 4.80 (m, 2H); 7.10 - 7.35 (m, 5H).

15 3-Methyl-5-(((2R)-2-(methylamino)-3-phenylpropoxy)methyl)-1,2,4-oxadiazole:



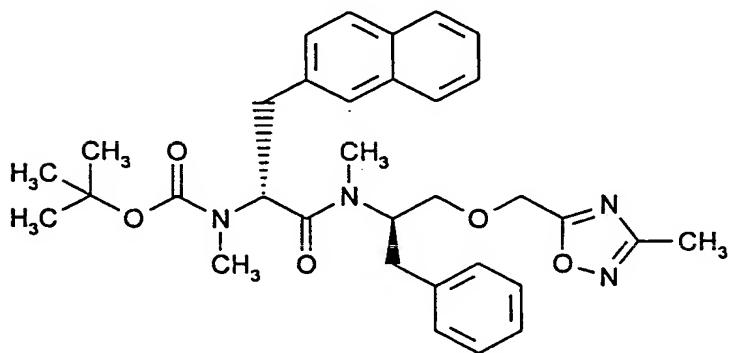
20 N-Methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl-2-phenylethyl)carbamcic acid tert-butylester (1.13 g; 3.13 mmol) was dissolved in dichloromethane (3 mL). The solution was cooled to 0°C. Trifluoroacetic acid (3 mL) was added. The solution was stirred at 0 °C for 5 min. The solvent was removed in vacuo without warming. The residue was dissolved in dichloromethane (100 mL)

25 and the solvent was removed in vacuo. This procedure was repeated twice. The crude product was purified by flash chromatography on silica (70 g) with dichloromethane/methanol/25% aqueous ammonia (100:10:1) to give 0.75 g of 3-methyl-5-(((2R)-2-(methylamino)-3-phenylpropoxy)methyl)-1,2,4-oxadiazole.

¹H-NMR (CDCl₃) δ 2.40 (s, 3H); 2.45 (s, 3H); 2.75 (dd, 1H); 2.85 (dd, 2H); 2.93 (m, 1H); 3.48 (dd, 1H); 3.56 (dd, 1H); 4.70 (AB, 2H); 7.15 - 7.35 (m, 5H)).

5

N-Methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butylester:



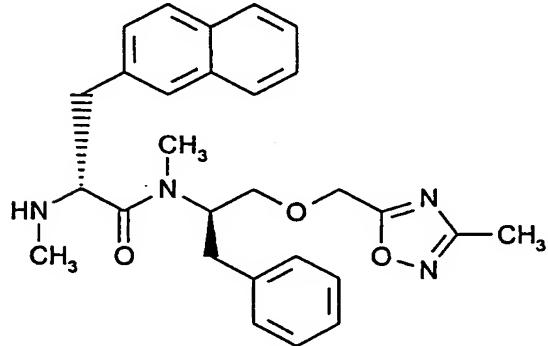
10

(2*R*)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-naphthyl)propionic acid (701 mg, 2.68 mmol) was dissolved in dichloromethane (4 mL) and N,N-dimethylformamide (4 mL). The solution was cooled to 0°C. 1-Hydroxy-7-azabenzotriazole (365 mg, 2.68 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (617 mg, 3.22 mmol) were successively added. The solution was stirred for 15 min at 0 °C. A solution of 3-methyl-5-((2*R*)-2-(methylamino)-3-phenylpropoxy)methyl)-1,2,4-oxadiazole (701 mg, 2.68 mmol) in dichloromethane (4 mL) was added. The reaction mixture was stirred for 16 hours, while the temperature slowly rose to room temperature. It was diluted with ethyl acetate (100 mL) and extracted with a mixture of saturated sodium chloride solution (50 mL) and water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (90 g) with ethyl acetate/heptane (2:1) to give 1.23 g of N-methyl-N-((1*R*)-1-

(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butylester.

5 ¹H-NMR (CDCl₃) δ 0.95, 1.02, 1.13, and 1.26 (all s, together 9H); 2.35 - 2.45 (m, 3H); 7.00 - 7.80 (m, 12H).

10 (2R)-2-(Methylamino)-3-(2-naphthyl)propionic acid N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)amide:

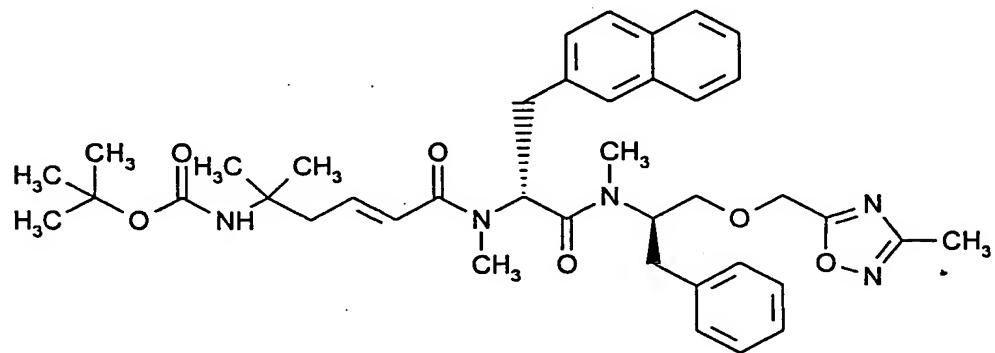


15 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)-methoxy)methyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butylester (1.21 g, 2.12 mmol) was dissolved in dichloromethane (4 mL). The solution was cooled to 0 °C. Trifluoroacetic acid (4 mL) was added. The solution was stirred for 12 min at 0 °C. The solvent was removed in vacuo without warming. The residue was dissolved in dichloromethane (150 mL), and the solvent was removed in vacuo. This latter procedure was repeated twice. The crude product was purified by flash chromatography on silica (70 g) with dichloromethane/methanol/25% aqueous ammonia (200:10:1) to give 497 mg of (2R)-2-(methylamino)-3-(2-naphthyl)propionic acid N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)amide.

¹H-NMR (DMSO d₆) δ 1.67 and 1.92 (both s, together 3H); 2.32 and 2.34 (both s, together 3H); 2.71 and 2.86 (both s, together 3H); 4.60 and 4.79 (both s, together 2H); 7.05 - 7.90 (m, 12H).

5

(3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadizol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enylcarbamic acid tert-butylester:



10

(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (258 mg, 1.06 mmol) was dissolved in dichloromethane (3 mL) and N,N-dimethylformamide (3 mL). 1-Hydroxy-7-azabenzotriazole (144 mg, 1.06 mmol) was added. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (260 mg, 1.36 mmol) was added. The solution was stirred for 15 min at 0 °C. A solution of (2R)-2-(methylamino)-3-(2-naphthyl)propionic acid N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)amide (456 mg, 0.97 mmol) in dichloromethane (3 mL) was added. The reaction mixture was stirred for 16 h, at room temperature. The reaction mixture was diluted with ethyl acetate (150 mL). It was washed with saturated sodium chloride solution (150 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (60 g) with ethyl acetate/heptane (2:1) to give 514 mg of (3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-

methyl-1,2,4-oxadizol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃) δ 1.05 - 1.50 (m, 15H); 6.05 (m, 1H); 6.55 and 6.74 (both m, s together 1H); 7.05 - 7.85 (m, 12H).

(3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadizol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enylcarbamic acid tert-butylester (464 mg, 0.66 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was cooled to 0 °C. Trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 7 min at 0 °C. The solvent was removed in vacuo. The residue was dissolved in dichloromethane (50 mL), and the solvent was removed in vacuo. This latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (30 g) with dichloromethane/methanol/25% aqueous ammonia (100:10:1). The product was dissolved in ethyl acetate (3 mL) and 3 M hydrogen chloride in ethyl acetate (0.7 mL) was added. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (50 mL) and the solvent was removed in vacuo to give 285 mg of the title compound as a hydrochloride.

20

HPLC: R_f = 35.40 min (Method A1)

¹H-NMR (DMSO-d₆) δ 1.03, 1.04, and 1.15 (all s, together 6H); 2.35 and 2.36 (both s, together 3H).

25

MS: 598.3 ([M+1]⁺)

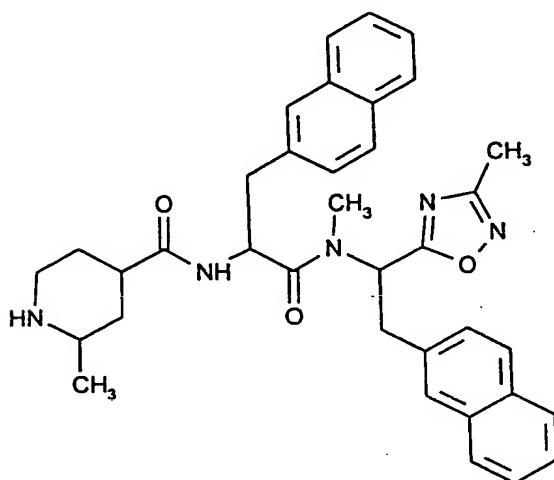


calc. C62.72 H7.22 N10.45

30 found C62.72 H7.04 N10.30

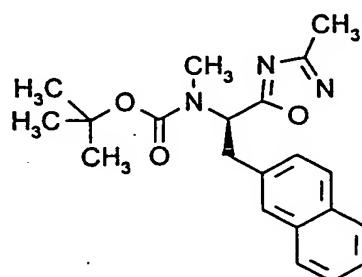
Example 27

5 2-Methyl-piperidine-4-carboxylic acid N-[1-[N-methyl-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl)carbamoyl]-2-(2-naphthyl)ethyl] amide:



10

(R) N-Methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamic acid tertbutyl ester:

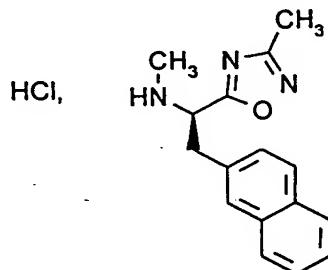


15

iso-Butylchloroformate (1.22 g, 9.0 mmol) was dropwise added to a solution of (R) N-methyl-N-tert-butoxycarbonyl-3-(2-naphthyl)alanine (3.0 g, 9 mmol) and N-

methylmorpholine (0.91 g, 9.0 mmol) in dichloromethane (40mL) at -20 °C. After 15 min at -20 °C acetamidoxim (1.33 g, 18 mmol) was added followed by addition of N-methyl-morpholine (0.91 g, 9 mmol). After 30 min at -20 °C the reaction mixture was heated to 20 °C and diluted with N,N-dimethylformamide (40 mL). The 5 dichloromethane was evaporated in vacuo and the reaction mixture was heated at 120° C for 16 hours. The reaction mixture was poured into water (120 mL) and extracted with ethyl acetate (180 mL). The organic phases were collected, washed with water (40 mL) and dried (magnesium sulfate). The solution was concentrated in vacuo to give 3.5 g of crude (R) N-methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-10 (2-naphthyl)ethyl]carbamic acid tertbutyl ester that was used without further purification.

(R) N-Methyl-N-[1(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]amine
15 hydrochloride:



(R) N-Methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamic acid tertbutyl ester (3.3 g, 9.0 mmol) was dissolved in a saturated solution of hydrogen chloride in ethyl acetate (75 mL). After 3 hours at 20 °C the reaction mixture was 20 filtered to give 1.52 g of (R) N-methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]amine hydrochloride.

m.p. 198-202 °C.

25 ¹H-NMR (DMSO-d₆) d 2.35(s, 3H); 2.68(s, 3H); 3.43(dd, 1H); 3.80(dd, 1H); 5.29(dd, 1H); 7.30(d, 1H); 7.45-7.90(m, 7H).

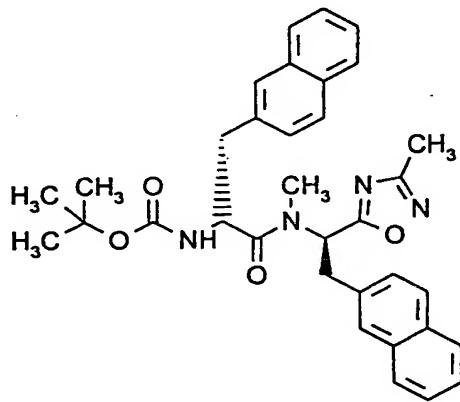
HPLC: R_f = 16.3 min (Method A1)

Calculated for C₁₆H₁₇N₃O₁,HCl:

C, 63.26; H, 5.97; N, 13.83%; found:

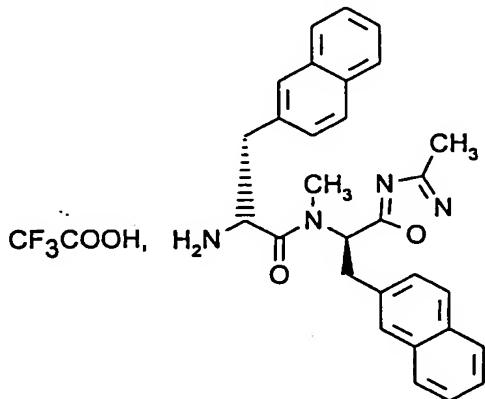
5 C, 63.37; H, 6.11; N, 13.53%.

{(1R)-1-{N-Methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-carbamoyl}-2-(2-naphthyl)ethyl}carbamic acid tertbutyl ester:



10 N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.12 g, 5.85 mmol) and 1-hydroxy-7-azabenzotriazole (0.8 g, 5.85 mmol) were added to a solution of (R) N-tert-butoxycarbonyl-3-(2-naphthyl)alanine (1.84 g, 5.85 mmol) in N,N-dimethylformamide (45 mL). After 30 min at 20 °C a mixture of (R) N-methyl-N-{1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl}amine hydrochloride (1.27 g, 4.18 mmol) and triethylamine (0.42 g, 4.18 mmol) in N,N-dimethylformamide (15 mL) were added. After 18 hours at 20 °C the reaction mixture was poured on water (200 mL) and extracted several times with ethyl acetate (110 mL). The combined organic phases were washed with aqueous citric acid (10%, 40 mL), a saturated solution of sodium hydrogen carbonate (3x40 mL) and water (3x40 mL). After 15 drying (magnesium sulfate) the solvent was concentrated in vacuo to give 2.4 g of crude {(1R)-1-{N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-carbamoyl}-2-(2-naphthyl)ethyl}carbamic acid tertbutyl ester which was used for the next step without further purification.

(2R)-2-Amino-N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)-ethyl]-3-(2-naphthyl)propionamide (as a trifluoroacetate):



5 {((1R)-1-{N-Methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-carbamoyl}-2-(2-naphthyl)ethyl)carbamic acid tertbutyl ester (2.4 g, 4.2 mmol) was dissolved in a mixture of trifluoroacetic acid (40 mL) and dichloromethane (40 mL) at 20°C. After 10 min the reaction mixture was concentrated in vacuo and coevaporated from dichloromethane (80 mL). The residue was crystallised from
 10 ethyl acetate to give 1.19 g of (2R)-2-amino-N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)-ethyl]-3-(2-naphthyl)propionamide, trifluoroacetic acid.

mp 190-191°C.

15

¹H-NMR (DMSO-d₆) δ 2.33(s, 3H); 2.88(s, 3H); 3.00-3.15(m, 2H); 3.45(dd, 1H); 3.65(dd, 1H); 4.71(t, 1H); 7.25-7.95(m, 14H).

HPLC: R_t = 24.3 min (Method A1)

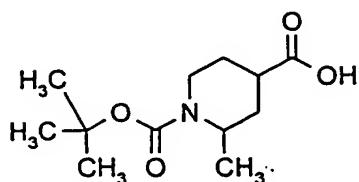
20

Calculated for C₂₉H₂₈N₄O₂, CF₃COOH:

C, 64.35; H, 5.05; N, 9.68%; found:

C, 64.30; H, 5.13; N, 9.44%.

2-Methylpiperidine-1,4-dicarboxylic acid 1-tert-butyl ester:



5

A suspension of 2-chloro-4-carboxy-6-methylpyridine (5.1 g, 3.0 mmol) in hydrochloric acid (1N, 50 mL) was hydrogenated over palladium on charcoal (20%, 0.95 g) at 150psi of hydrogen at 60°C for 18 hours. The reaction mixture was filtered and concentrated in vacuo. The crude product was dissolved in aqueous sodium hydroxide (1N, 53 mL) and a solution of di-tert-butyloxocarbonyl (6.35 g, 29.1 mmol) in tetrahydrofuran (30 mL) was added. After 3 days at room temperature the reaction mixture was extracted with diethyl ether (50 mL) at pH 10. The aqueous phase was adjusted to pH 2 with sulfuric acid (1N, 30 mL) and extracted with ethyl acetate (30 mL). The organic phase was washed with water (4x15 mL), dried (magnesium sulfate) and concentrated in vacuo. The residue was chromatographed on silica (105 g) using ethyl acetate and heptane (1:1) as eluent to give 1.8 g of 2-methylpiperidine-1,4-dicarboxylic acid 1-tert-butyl ester.

M.p. 109-112°C

20 ¹H-NMR (DMSO-d₆) δ 1.13(d, 3H); 1.42(s, 9H); 1.70(m, 1H); 1.95(m, 2H); 2.60(m, 1H); 3.12(m, 1H); 3.31(s, 1H); 3.77(m, 1H); 4.15(m, 1H); 12.25 (s, 1H).

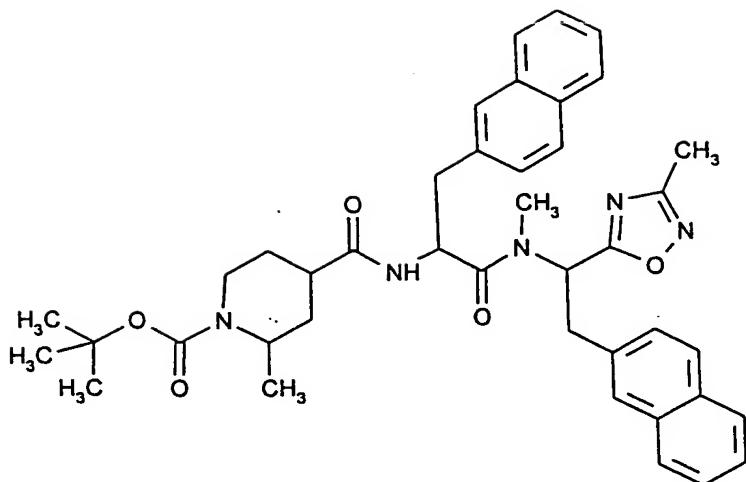
Calculated for C₁₂H₂₁N₁O₄:

C, 59.24; H, 8.70; N, 5.76%; found:

C, 59.39; H, 9.13; N, 5.58%.

25

4-(1-{Methyl-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)carbamoyl)-2-methylpiperidine-1-carboxylic acid tert-butyl ester:



L
O
G
I
C
S
C
E
D
D
R
E

N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.46 g, 2.42 mmol) and 1-hydroxy-benzotriazole monohydrate(0.37 g, 2.41 mmol) were added to a 5 solution of 2-methylpiperidine-1,4-dicarboxylic acid-1-tert-butylester (0.59 g, 2.42 mmol) in N,N-dimethylformamide (8 mL). After 30 min at 20°C a solution of (2R)-2-amino-N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-3-(2-naphthyl)propionamide (as a trifluoroacetate) (1.0 g, 1.73 mmol) and diisopropylethylamine (0.22 g, 1.73 mmol) in N,N-dimethylformamide (4 mL) was 10 added. After 18h at 20°C the reaction mixture was poured on water (100 mL) and extracted several times with ethyl acetate (total 60 mL). The collected organic phases were washed with aqueous citric acid (10%, 20 mL), a saturated solution of sodium hydrogen carbonate (20 mL) and water (3x20 mL). After drying (magnesium sulfate) the solution was concentrated in vacuo to give 1.25g of crude 15 4-(1-{methyl-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)-carbamoyl)-2-methylpiperidine-1-carboxylic acid tert-butyl ester that was used for the next step without further purification.

HPLC: $R_t = 35.8\text{min}$ (Method A1)

g, 1.81 mmol) was dissolved in a mixture of trifluoroacetic acid (5 mL) and dichloromethane (5 mL). After 10 min at 20°C the reaction mixture was quenched with a saturated solution of sodium hydrogen carbonate (45 mL) and extracted with dichloromethane (60 mL). The organic phases were collected, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was chromatographed on silica gel (105 g) using a 10% mixture of ammonia in ethanol and dichloromethane (1:9) as eluent to give 0.90 g of the title compound, which was finally lyophilised in 10% acetic acid.

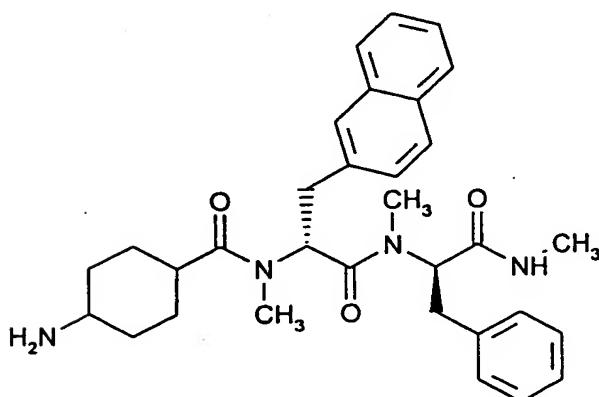
10 HPLC: R_f = 24.3 min (Method A1)

PDMS: calculated: 589.7 [M]

found: 589.5 ± 1 [M+1]

15 Example 28

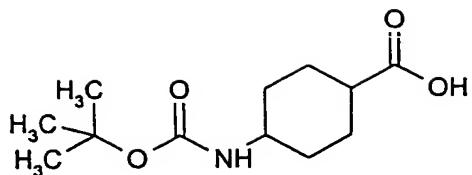
4-Amino-cyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N- methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl]carbamoyl]-2-(2-naphthyl)ethyl)amide:



20

4-tert-Butoxycarbonylamino-cyclohexanecarboxylic acid:

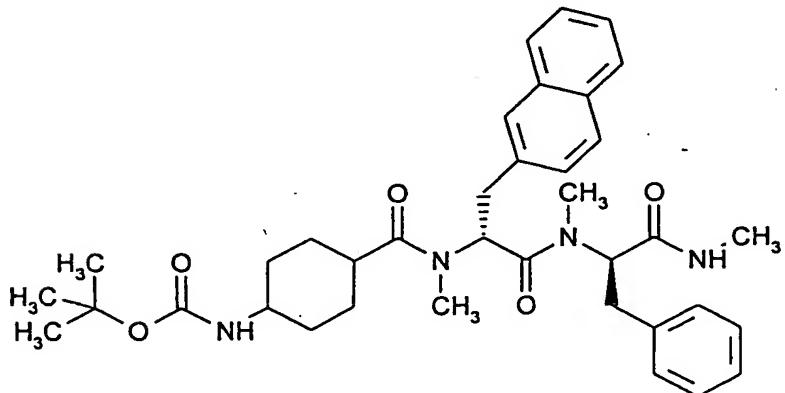
25



To a suspension of 4-aminocyclohexane carboxylic acid (3.0 g, 20.95 mmol) in
 5 dioxan (40 mL) and water (20 mL) was added 20 ml of a 1 M sodium hydroxide
 solution. Di-tert-butyl dicarbonate (5.0 g, 23.05 mmol) was added and the mixture
 was stirred overnight. The mixture was concentrated in vacuo to 30 ml of solvent
 and 60 ml of ethyl acetate was added and the mixture was cooled to 0°C. The
 mixture was acidified to pH 2 with sodium bisulfate and the aqueous phase was
 10 extracted with ethyl acetate (2 x 100 ml). The combined organic phases were
 washed with water (100 ml) and dried over magnesium sulfate and concentrated in
vacuo to give 4.13 g of 4-tert-butoxycarbonylamino cyclohexane carboxylic acid.

1H-NMR (DMSO-d₆): δ_H 1.3 (s, 9H) 1.3-1.6 (m, 5H) 1.9 (m, 3H), 2.3 (m, 1H) 6.7 (m,
 15 1H)

(4-[N-Methyl-N-{(1R)-1-(N-methyl-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]-
 carbamoyl)-2-(2-naphthyl)ethyl}carbamoyl]cyclohexyl)carbamic acid tert-butyl ester:



20

To a suspension of 4-tert-butoxycarbonylamino cyclohexane carboxylic acid (115 mg, 0.47) in 5 ml of dichloromethane was added 1-hydroxy-7-azabenzotriazole (64 mg, 0.47 mmol) in 0.5 ml N,N-dimethylformamide. 1-Ethyl-3-(3-

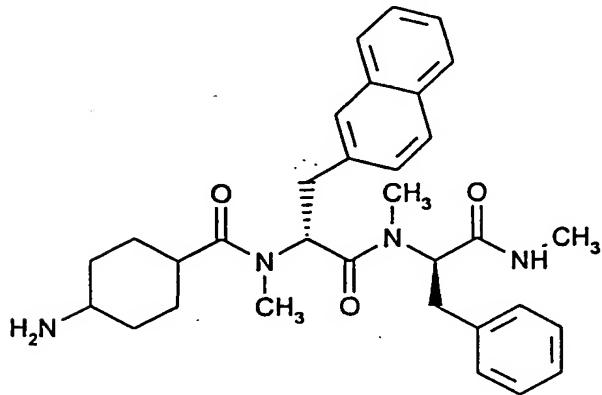
dimethylaminopropyl)carbodiimide hydrochloride (100 mg, 0.52) was added and the solution was stirred for 20 min. Diisopropylethylamine (120 mg, 0.94 mmol) and N-methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (191 mg, 0.47 mmol) in 5 ml of dichloromethane was added 5 and the mixture was allowed to stand overnight at room temperature. The mixture was washed with water (5 ml), sodium bicarbonate (5 ml) water (2 x 5 ml) and brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (20 g) with ethyl acetate as eluent to give 242 mg of (4-[N-Methyl-N-{(1R)-1-(N-methyl-[{1R}-1-(methylcarbamoyl)-2-

10 phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]-carbamoyl]cyclohexyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): δ 1.0-1.8 (m, 8H) 1.5 (d, 9H) 2.4 (s, 3H) 2.7-3.3 (m, 4H) 2.9 (s, 3H) 3.0 (s, 3H) 3.7 (m, 1H) 4.6 (m, 1H) 5.2-5.8 (m, 2H) 7.0-7.8 (m, 12H)

15

4-Amino-cyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N-methyl-N-{(1R)-1-methylcarbamoyl-2-phenylethyl}-carbamoyl]-2-(2-naphthyl)ethyl)amide:



20 To a solution of (4-[N-Methyl-N-{(1R)-1-(N-methyl-[{1R}-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)-ethyl]-carbamoyl]cyclohexyl)carbamic acid tert-butyl ester (240 mg, 0.38 mmol) in 1 ml dichloromethane was added 0.5 ml trifluoroacetic acid and the mixture was stirred for 5 min. Sodium bicarbonate was added until gas evolution has ceased, and the mixture was extracted with 25 dichloromethane (3 x 15 ml). The combined organic phases were washed with

brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (16 g) with dichloromethane/methanol (4:1). The obtained product was dissolved in 3 ml of methanol and added 40 ml of water and 0.5 ml of acetic acid and lyophilized to give 99 mg of the title compound.

5

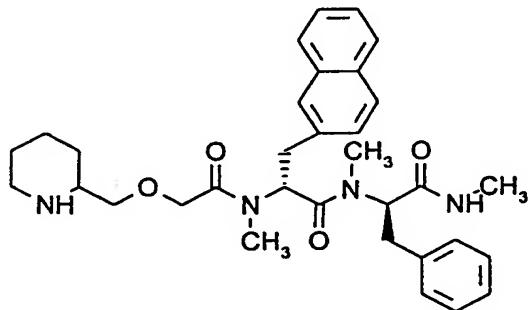
¹H-NMR (DMSO-d₆), (free base): d 1.2-1.5 (m, 8H) 2.05 (s, 3H) 2.65 (d, 3H) 2.7 (s, 3H) 2.5-3.3 (m, 6H) 5.4 (m, 1H) 5.6 (m, 1H) 7.1-7.8 (m, 12H)

HPLC: R_t = 30.2 min (method A1)

10

Example 29

N-Methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-2-(N-methyl-N-15 {[[(2-piperidinyl)methoxy]acetyl}amino)-3-(2-naphthyl)propinamide:



2-(Carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester:

20 <img alt="Chemical structure of 2-(Carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester. It consists of a piperidine ring substituted with a methylene group (-CH<sub>2-). The methylene group is attached to a carboxylic acid group (-COOH) and a methoxymethyl group (-CH₂OCH₃). Below the piperidine ring is a tert-butyl ester group (-C(CH₃)₃).

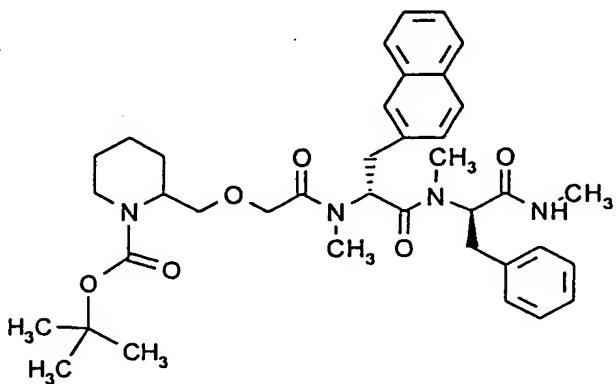
To a solution of N-(tert-butoxycarbonyl)-2-hydroxymethylpiperidine in 500 ml of dichloroethane was added 180 mg of rhodium(II)acetate and the mixture was

heated to 80 °C. Ethyldiazoacetate (3.7 ml, 35 mmol) in 180 ml dichloroethane was added (during approx. 1 hour) and stirred at 80°C for 6 hours. Another portion of ethyldiazoacetate (1.25 ml, 12 mmol) in 40 ml of dichloroethane was added (over 20 min) and the mixture was refluxed at 80°C for 7 h. The mixture was cooled to room temperature and washed with sodium bicarbonate (150 ml) and brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (100 g) with pentane:ethyl acetate (4:1) as eluent to give 2.64 g of 2-(((ethoxycarbonyl)methoxy)methyl)piperidine-1-carboxyl acid tert-butylester. The obtaining product was taken up in 40 ml of 1 M LiOH in water:methanol (1:3) and stirred at room temperature for 30 min. The mixture was concentrated in vacuo and water (20mL) was added and the solution was washed with ether (20mL). The aqueous phase was acidified to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (50 ml), dried over magnesium sulfate and concentrated in vacuo to give 2.41 g of 2-(carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester.

MHz-¹H-NMR (CDCl₃): d 1.45 (s, 9H) 1.55 (m, 2H) 1.85 (m, 2H) 3.1 (m, 2H) 3.6 (m, 1H) 3.8 (m, 2H) 4.15 (s, 2H)

20

2-([N-Methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]-carbamoyl)-2-(naphthyl)ethyl]carbamoyl)methoxymethyl)piperidin-1-carboxylic acid tert-butyl ester:



To a solution of 2-(carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester (225 mg, 0.82 mmol) in 5 ml of dichloromethane was added 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol) and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (173 mg, 0.90 mmol) and the mixture was stirred for 30 min. N-Methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (332 mg, 0.82 mmol) in dichloromethane (5mL) was added followed by diisopropylethylamine (0.14 ml, 0.82 mmol) and the mixture was stirred overnight at room temperature. The mixture was washed with water (5 ml) aqueous sodium bicarbonate (5 ml), water (2 x 5 ml), brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (20 g) with ethyl acetate to give 416 mg of 2-([N-methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl)methoxymethyl)piperidin-1-carboxylic acid tert-butyl ester.

15

¹H-NMR (CDCl₃) (selected peaks): d 1.45 (s, 9H) 2.45 (d, 3H) 2.75 (d, 3H) 2.90 (d, 3H) 3.0 (s, 2H)

20 To a solution of 2-([N-methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl)methoxymethyl)piperidin-1-carboxylic acid tert-butyl ester (388 mg, 0.60 mmol) in dichloromethane (1mL) was added trifluoroacetic acid (1mL) and the mixture was stirred for 10 min at room temperature. Then saturated sodium bicarbonate was added until pH 8 and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (15 g) with dichloromethane:methanol (9:1) to give 273 mg of the title compound.

25

¹H-NMR (CDCl₃) (selected peaks): d 5.3 (m, 1H) 5.75 (t, 1H) 7.0-7.8 (m, 12H)

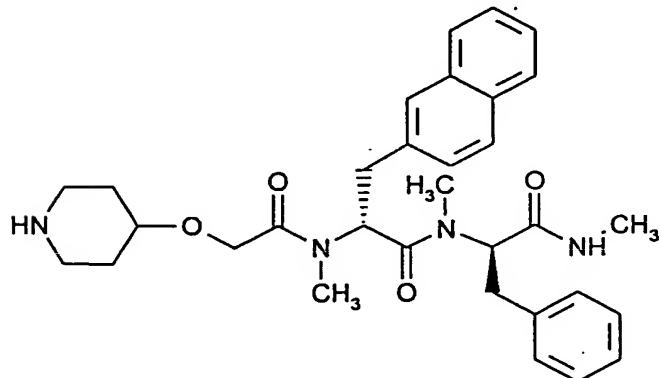
EI/SPMS : 559.5 (M+)

HPLC: $R_t = 32.0$ (Method A1)

5

Example 30

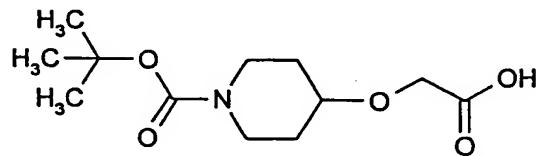
(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(methyl{[piperidin-4-yloxy]acetyl}amino)-3-(2-naphthyl)propionamide:



10

4-(Carboxymethoxy)piperidine-1-carboxylic acid tert-butyl ester:

15



To a solution of 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (5.0 g, 25 mmol) and rhodium(II)acetate (180 mg) in 500 ml dichloroethane at 80°C was added (over 90 min) ethyl diazoacetate (4.2 ml, 50 mmol) in 220 ml dichloroethane. The mixture was stirred for 7 h and quenched with aqueous sodium bicarbonate (2 x 100 ml). The organic phase was isolated and washed with brine (2 x 100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (80g) in petroleum ether:ethyl acetate (4:1) to give 3.4 g

of 4-(ethoxycarbonylmethoxy)piperidine-1-carboxylic acid tert-butylester. The product was taken up in 40 ml of a 1 M lithium hydroxide solution in water:methanol (1:3) and stirred for 60 min. The mixture was concentrated in vacuo and dissolved in 20 ml of water, acidified to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine (10 ml), dried over magnesium sulfate and concentrated in vacuo to give 1.79 g of 4-(carboxymethoxy)piperidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃): δ 1.45 (s, 9H) 1.55 (m, 2H) 1.9 (m, 2H) 3.1 (m, 2H) 3.6 (m, 1H)
3.8 (m, 2H) 4.2 (s, 2H)

A solution of 4-(carboxymethoxy)piperidine-1-carboxylic acid tert-butyl ester (228 mg, 0.88 mmol), 1-hydroxy-7-azabenzotriazole (120 mg, 0.88 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (186 mg, 0.97 mmol) was stirred for 30 min at room temperature. N-Methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(naphthalen-2-yl)propionamide (355 mg, 0.88 mmol) in 5 ml of dichloromethane was added followed by diisopropylethylamine (0.2 ml, 1.14 mmol) and the mixture was stirred for 2 days at room temperature. The mixture was washed with water (5 ml) aqueous sodium bicarbonate (5 ml), water (2 x 5 ml), brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (30 g) with ethyl acetate as eluent to give 391 mg of 4-([N-methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methyl carbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl)methoxy]piperidin-1-carboxylic acid tert-butylester. The product was taken up in 50% trifluoromethane/dichloromethane and allowed to stand for 10 min. Then saturated sodium bicarbonate was added until pH was about 8 and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (15 g) with dichloromethane:methanol (9:1) to give 327 mg of the title compound.

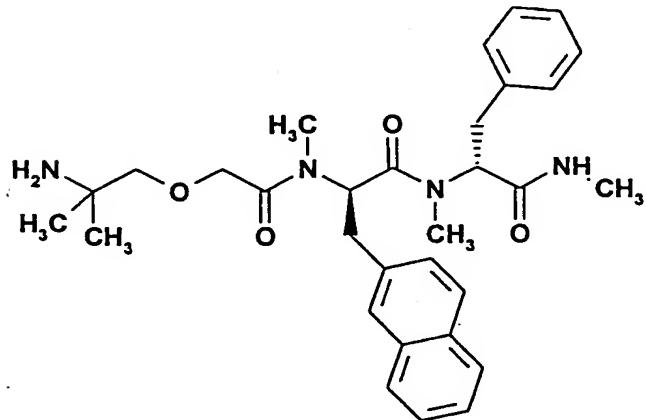
¹H-NMR (CDCl₃) (selected peaks): d 3.75 (q, 2H) 5.5 (m, 1H) 5.8 (t, 1H) 7.0-7.8 (m, 12H)

5 EI/SPMS: 544.5 (M⁺)

HPLC: R_t = 28.9 (Method A1)

10 Example 31

2-[1-Methyl-2-(2-amino-(2-methylpropoxy))acetylamino]-N-(1-methyl-1-((1-methylcarbamoyl)-2-(2-phenylethyl)-3-(2-naphthyl))propionamide:



15

A solution of 2-t-butoxycarbonylamino-2-methylpropanol (5.0 g, 26.46 mmol) and rhodium(II)acetate (90 mg) in dichloroethane (500 mL) was heated to 80 °C. Ethyldiazoacetate (4.0 g, 34.78 mmol) was slowly added over a period of 1 hr., 20 and the mixture was stirred at reflux for 3 hr. Another 90 mg of rhodium(II)acetate was added and the mixture was refluxed for another 5 hr. The mixture was cooled overnight and 500 ml of saturated sodium bicarbonate was added, the yellow organic layer was separated and washed twice with saturated sodium bicarbonate (2 x 200 ml). The organic layer was dried over magnesium sulfate and 25 concentrated in vacuo. The yellow oil was taken up in 200 ml of 1 M Lithium

hydroxide in methanol:water (3:1) and stirred overnight. The solvent was removed in vacuo to a minimum and water was added (pH>9) and the mixture was washed with ether. Then 1 M hydrogen chloride was added until pH<4 and the mixture was extracted with ethyl acetate, dried over magnesium sulfate and concentrated
5 in vacuo to give 2.5 g (38%) of (2-t-butoxycarbonylamino-2-methylpropoxy) acetic acid as a clear oil.

H¹-NMR (CDCl₃, 400 MHz) δ 1.3 (s, 6H); 1.45 (s, 9H); 3.5 (s, 2H); 4.15 (s, 2H);
9.9 (b, 1H).

A solution of (2-tert-butoxycarbonylamino-2-methylpropoxy) acetic acid (184 mg, 0.74 mmol), 1-hydroxy-7-azobenzotriazole (101 mg, 0.74 mmol) and 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloric acid (157 mg, 0.82 mmol) in 9 ml of methylene chloride and 1 ml of DMF was stirred for 15 min. Then N-methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(naphthalen-2-yl)propionamide (300 mg, 0.74 mmol) and diisopropylethylamine (96 mg, 0.74 mmol) in 1 ml of methylene chloride were added and allowed to stir overnight. The mixture was washed with saturated sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo. The mixture was chromatographed on 100 ml of silica gel
10 with ethyl acetate to give 360 mg (76 %) of 2-[1-methyl-2-(2-(t-butoxycarbonyl)amino-(2-methylpropoxy))acetyl]amino]-N-(1-methyl-1-((1-methylcarbamoyl)-2-(2-phenylethyl)-3-(2-naphthyl))propionamide. The obtained mixture was taken up in 1 ml of TFA and 1 ml of methylene chloride and stirred at 0°C for 5 min. Then saturated sodium bicarbonate was slowly added to the cooled solution and the
15 organic layer was separated, washed with sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo to give 185 mg (47% from (2-t-butoxycarbonylamino-2-methylpropoxy) acetic acid) of 2-[1-methyl-2-(2-amino-(2-methylpropoxy))acetyl]amino]-N-(1-methyl-1-((1-methylcarbamoyl)-2-(2-phenylethyl)-3-(2-naphthyl))propionamide as an oil. The obtained oil was dissolved in
20 0.1 N acetic acid (50 ml) and lyophilized to give an amorph white powder.
25

¹H-NMR (CDCl₃, 400 MHz, free amine) δ 0.9 (d, 3H); 1.05 (d, 3H); 2.35 (s, 3H); 2.75 (s, 3H); 2.8 (s, 3H); 2.9 (s, 2H); 3.0 (s, 2H); 3.0-2.7 (m, 2 H); 3.25 (m, 2H); 3.7 (t, 1H); 5.1 (dd, J=20 Hz, 1H); 5.8 (t, 1H, amine); 7.8-6.9 (m, 12H).

5

HPLC: Rt = 30.65 min in A1; 97 % purity

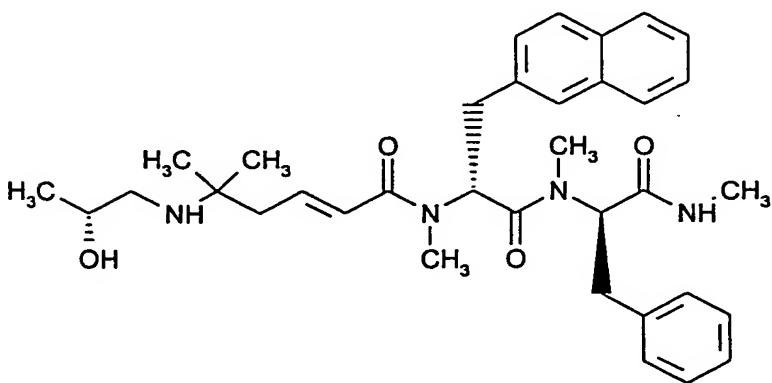
Calculated for C₃₁H₄₀N₄O₄, CH₃COOH, H₂O:

C, 64.9 %; H, 7.6 %; N, 9.1 %; Found:

10 C, 64.2 %; H, 7.6 %; N, 8.5 %

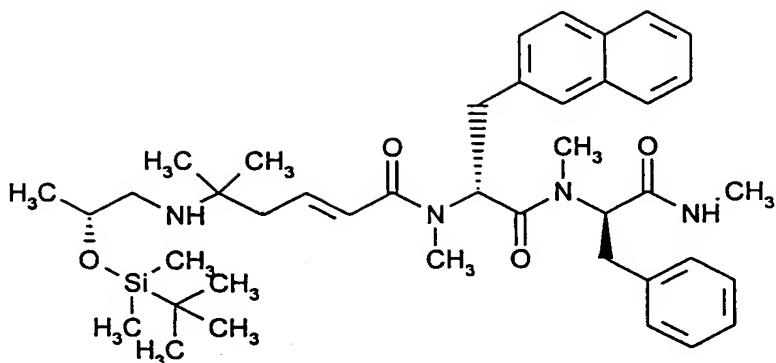
Example 32

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-Hydroxypropylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;



20

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-(tert-Butyldimethylsilyloxy)propylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;



5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide (318 mg, 0.60 mmol) was dissolved in methanol (20 ml) and glacial acetic acid (0.48 ml, 8.4 mmol). 3 Å mol sieves (9 g) and a solution of (2R)-2-(tert-

- 10 butyldimethylsilyloxy)propanal (1.33 g, 7.06 mmol) in methanol (10 ml) were added successively. Sodium cyanoborohydride (220 mg, 3.53 mmol) was added as a solid. The reaction mixture was stirred at room temperature for 45 min, before a second batch of sodium cyanoborohydride (220 mg, 3.53 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. The mol sieves was
- 15 filtered off through a plug of celite. The celite was washed with methanol (200 ml). The solvents of the combined filtrates were removed in vacuo. The residue was dissolved in 1 N sodium hydroxide solution (50 ml) and tert-butyl methyl ether (50 ml). The phases were separated. The aqueous phase was extracted with tert-butyl methyl ether (3 x 50 ml). The combined organic layers were dried over magnesium
- 20 sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (35 g), using ethyl acetate/heptane/triethylamine (20:10:1) as eluent, to give 99 mg of (2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-(tert-butyldimethylsilyloxy)propylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide.

¹H-NMR (CDCl₃, selected values): d 0.04, 0.05, and 0.10 (all s, together 6 H); 0.85 and 0.91 (both s, together 9 H); 3.86 (m, 1 H); 6.04 and 6.08 (both d, together 1 H); 6.89 (m, 1 H).

5 MS: 701.2 [M+1].

HPLC: The RP-analysis was performed using UV detections at 214, 254, 276, and 301 nm on a 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1 mL/min at 42°C. The column was
 10 equilibrated with 5% acetonitrile in a buffer consisting of 0.1% aqueous trifluoro acetic acid eluted by a gradient of 0% to 90% of 0.1% trifluoro acetic acid in acetonitrile during 50 min: R_t = 37.25 min.

15

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-(tert-Butyldimethylsilyloxy)propylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide (99 mg, 0.14 mmol) was dissolved in tetrahydrofuran (2 ml). Tetra-n-butylammonium fluoride (0.18 ml of a 1.1 M solution in
 20 tetrahydrofuran, 0.2 mmol) was added. The solution was stirred for 3 h, before another portion of tetra-n-butylammonium fluoride (0.23 ml of a 1.1 M solution in tetrahydorfuran, 0.25 mmol) was added. The reaction mixture was stirred for 2.5 h at room temperature and diluted with ethyl acetate (50 ml). It was extracted with 10% sodium carbonate solution (30 ml). The aqueous phase was extracted with
 25 ethyl acetate (20 ml). The organic layers were combined and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash-chromatography on silica (30 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 28 mg of the title compound.
 30 ¹H-NMR (CDCl₃, selected values): d 3.65 and 3.72 (both m, together 1 H); 5.15 and 5.30 (both dd, together 1 H); 5.60 and 5.90 (both dd, together 1 H); 6.03 and 6.05 (both d, together 1 H); 6.78 (m, 1 H).

MS: 587.2 [M+1].

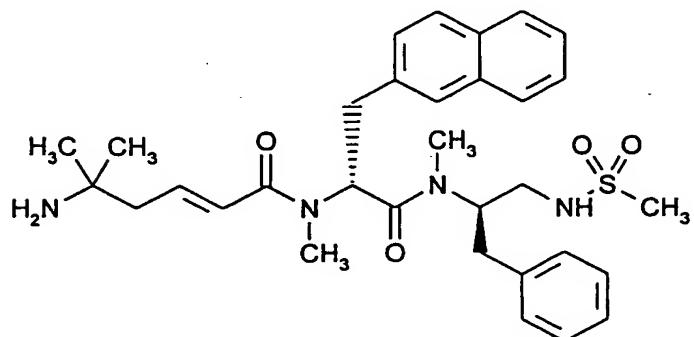
HPLC: $R_t = 27.47$ (A1).

5 $R_t = 27.12$ (B1).

For biological testing it was transferred into the acetate by lyophilization from 0.5 M
10 acetic acid (20 ml).

Example 33

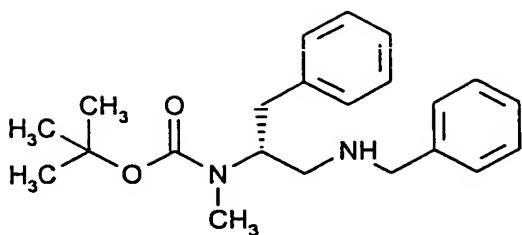
(2E)-5-Amino-N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-
15 methylcarbamoyl)-2-(2-naphthyl)ethyl)-5-methyl-N-methylhex-2-enamide;



20

N-((1R)-1-Benzyl-2-(benzylamino)ethyl)-N-methylcarbamic acid tert-butylester;

25



5 A solution of oxalyl chloride (3.16 ml, 36.17 mmol) in dichloromethane (50 ml) was cooled to -78 °C. A solution of dimethylsulfoxide (3.42 ml, 48.22 mmol) in dichloromethane (50 ml) was added dropwise. The reaction mixture was stirred for 5 min at -78 °C. A solution of N-((1R)-1-(hydroxymethyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester (6.40 g, 24.11 mmol) in dichloromethane (100 ml) was added dropwise over a period of 10 min. The solution was stirred for 25 min at -78 °C. Ethyldiisopropylamine (16.68 ml, 96.44 mmol) was added dropwise at -78 °C. The solution was warmed to -35 °C, and immediately cooled to -78 °C. Glacial acetic acid (6.07 ml, 106.08 mmol) was added. The reaction mixture was warmed to room temperature and diluted with dichloromethane (150 ml). It was washed with saturated sodium chloride solution (2 x 200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was dissolved in methanol (200 ml). Benzylamine (2.6 ml, 24.1 mmol) was added. Glacial acetic acid (6.0 ml, 106 mmol) and 3 Å mol sieves (32 g) were added. Sodium cyanoborohydride (1.00 g, 15.9 mmol) was added as a solid. The reaction mixture was stirred for 1h, before another portion of sodium cyanoborohydride (0.97 g, 15.4 mmol) was added. The mixture was first stirred for 16 h at room temperature and successively left 3 days without stirring. The mol sieves was filtered off through a plug of celite. The celite was washed with methanol (200 ml). The solvent was removed in vacuo. The residue was dissolved in 1 N sodium hydroxide solution/diethyl ether (250 ml/250 ml). The phases were separated. The aqueous phase was extracted with diethyl ether (2 x 100 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (230 g), using

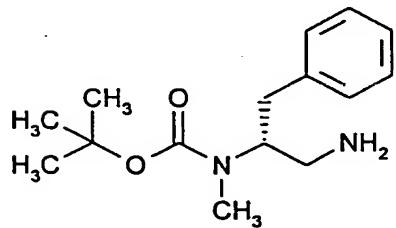
dichloromethane/methanol/25% aqueous ammonia (first 100:10:1, then 50:10:1) as eluent, to give 4.54 g of N-((1R)-1-benzyl-2-(benzylamino)ethyl)-N-methylcarbamic acid tert-butylester.

5 ¹H-NMR (CDCl₃): d 1.28 and 1.36 (both br, together 9 H); 2.50 - 2.90 (m, 8 H); 3.70 (d, 1 H); 3.88 (d, 1 H); 4.45 and 4.65 (both br, together 1 H); 7.10 - 7.40 (m, 10 H).

MS: 355.2 [M+H]⁺.

10

N-((1R)-1-Aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester;



15

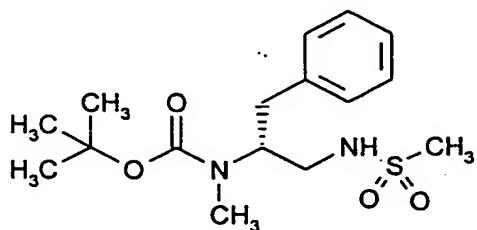
A suspension of 20% palladium hydroxide on charcoal (4.63 g) and N-((1R)-1-benzyl-2-(benzylamino)ethyl)-N-methylcarbamic acid tert-butylester (4.40 g, 12.4 mmol) was kept for 8 h under a hydrogen atmosphere at (pressure: 1 atm). The 20 reaction mixture was flushed with nitrogen and filtered through a plug of celite. The solvent was removed. The crude product was purified by flash chromatography on silica (110 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 830 mg of N-((1R)-1-aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

25

¹H-NMR (CDCl₃): d 1.29 and 1.36 (both s, together 9 H); 1.40 (s, 2 H); 2.60 - 2.90 (m, 7 H); 4.20 and 4.38 (both br, together 1 H); 7.10 - 7.35 (m, 5 H).

N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamic acid tert-butylester;

5



N-((1R)-1-Aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester (830 mg, 3.14 mmol) was dissolved in dichloromethane (15 ml). Triethylamine (0.44 ml, 3.14 mmol) was added. The solution was cooled to -78 °C. A solution of methanesulfonyl chloride (0.24 ml, 3.14 mmol) in dichloromethane (2 ml) was added dropwise. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with dichloromethane (100 ml) and washed with saturated sodium chloride solution (100 ml). It was dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (65 g), using ethyl acetate/heptane (2:1) as eluent, to give 990 mg of N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamic acid tert-butylester.

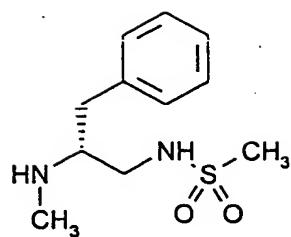
20

¹H-NMR (CDCl₃): d 1.30 and 1.40 (both br, together 9 H); 2.60 - 3.00 (m, 5 H); 2.93 (br, 3 H); 3.15 - 3.50 (m, 2 H); 4.40 (br, 1 H); 4.50 and 4.70 (both br, together 1 H); 7.05 - 7.35 (m, 5 H).

25

N-((2R)-2-Methylamino-3-phenylpropyl)methansulfonamide;

 ESTATE
SOLVENT
D
N
C
R

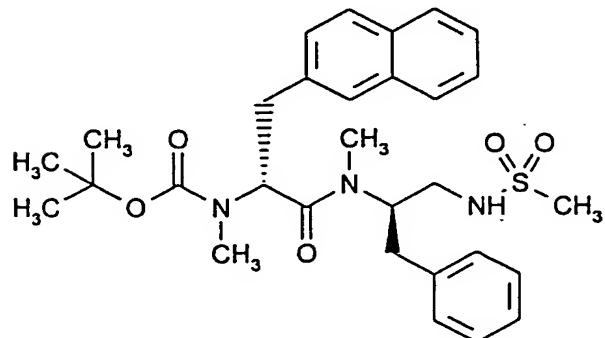


At 0 °C, trifluoroacetic acid (5 ml) was added to a solution of N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamic acid tert-butylester (913 mg, 2.67 mmol) in dichloromethane (5 ml). The reaction mixture was stirred for 15 min at 0 °C. The solvent was removed in vacuo without warming. The residue was dissolved in dichloromethane (50 ml) and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (20 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 658 mg of N-((2R)-2-methylamino-3-phenylpropyl)methansulfonamide.

¹H-NMR (CDCl₃, selected values): δ 2.39 (s, 3 H); 2.70 - 3.00 (m, 4 H); 2.95 (s, 3 H); 3.22 (dd, 1 H), 7.15 - 7.35 (m, 5 H).

15

N-((1R)-1-(N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester;

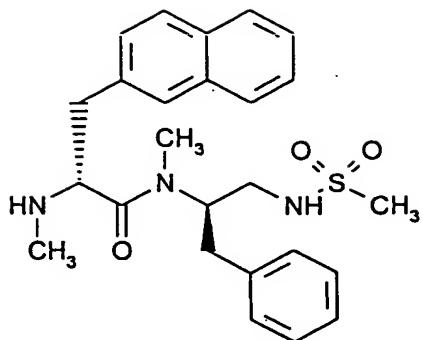


20

(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (1.05 g, 3.2 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). Hydroxy-7-azabenzotriazole (434 mg, 3.2 mmol) was added as a solid. The
5 solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (612 mg, 3.2 mmol) was added. The solution was stirred for 5 min at 0 °C. A solution of N-((2R)-2-methylamino-3-phenylpropyl)methanesulfonamide (703 mg, 2.9 mmol) in dichloromethane (2 ml) was added. Ethyldiisopropylamine (0.50 ml, 2.90 mmol) was added. The solution was stirred for 27 h, while it was warming
10 up to room temperature. It was diluted with ethyl acetate (200 ml) and extracted with 1 N hydrochloric acid (100 ml). The aqueous phase was extracted with ethyl acetate (50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on
15 silica (45 g), using ethyl acetate/heptane (2:1) as eluent, to give 1.037 g of N-((1R)-1-(N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃, selected values): d 1.30 and 1.34 (both br, together 9 H); 7.00 -
20 7.90 (m, 12 H).

N-((2R)-2-(N-Methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropyl)methanesulfonamide;



DRAFT - DO NOT CITE

At 0 °C, trifluoroacetic acid (4 ml) was added to a solution of N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester (997 mg, 1.8 mmol) in dichloromethane (4 ml).

The solution was stirred for 15 min at 0 °C. The solvent was removed in vacuo at 20 °C. The residue was dissolved in dichloromethane and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (45 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 646 mg of N-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropyl)methanesulfonamide.

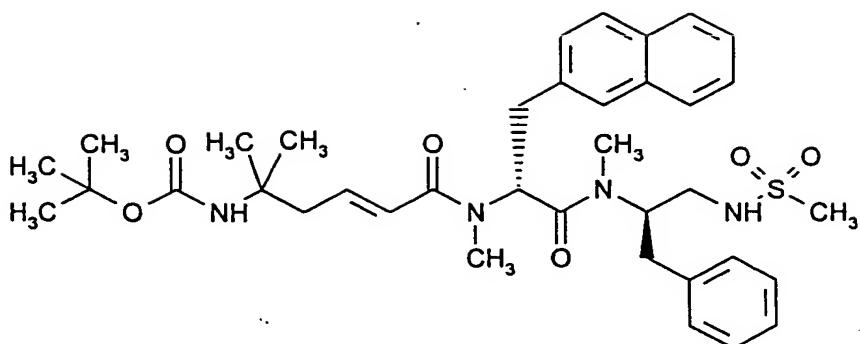
¹⁵ ¹H-NMR (CDCl₃, selected values): δ 1.87, 2.33, 2.38, 2.50, 2.62, 2.80, 2.82, 2.88, and 2.92 (all s, together 9 H); 3.62 and 3.76 (both dd, together 1 H); 4.56 and 4.72 (both br, together 1 H); 4.84 and 5.02 (both br, together 1 H); 6.90 - 7.95 (m, 12 H).

MS: 454.2 [M+H]⁺.

20

(3E)-4-(N-((1R)-1-(N-((1R)-1-Benzyl-2-(methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butyl ester;

25



ପ୍ରକାଶକ ପତ୍ର ମାତ୍ର

s (2E)-5-tert-Butoxycarbonylamino-5-methylhex-2-enoic acid (352 mg, 1.45 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). Hydroxy-7-azabenzotriazole (197 mg, 1.45 mmol) was added as a solid. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (278 mg, 1.45 mmol) was added. The solution was stirred for 15 min
 10 at 0 °C. A solution of N-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropyl)methanesulfonamide (598 mg, 1.32 mmol) in dichloromethane (2 ml) and ethyldiisopropylamine (0.23 ml, 1.32 mmol) were added successively. The solution was stirred for 18 h, while it was warming up to room temperature. It was diluted with ethyl acetate (100 ml) and extracted with 1
 15 N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (60 g), using ethyl acetate/heptane (2:1) as eluent to give 740 mg of (3E)-4-
 20 (N-((1R)-1-(N-((1R)-1-benzyl-2-(methylsulfonylamino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl_3 , selected values): δ 2.60, 2.80, 2.89, 2.92, 3.06, and 3.17 (all s, together 9 H); 6.06 and 6.25 (both d, together 1 H); 6.82 and 6.96 (both m, together

1 H); 7.00 - 7.85 (m, 12 H).

(3E)-4-(N-((1R)-1-(N-((1R)-1-Benzyl-2-(methylsulfonylamino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butyl ester (729 mg, 1.07 mmol) was dissolved in dichloromethane (3 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (3 ml) was added. The reaction mixture was stirred for 15 min at 0 °C. The solvents were removed in vacuo at 20 °C. The residue was dissolved in dichloromethane (100 ml) and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (60 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 440 mg of the title compound as free base.

¹⁵ ¹H-NMR (CDCl₃, selected values): δ 1.10, 1.11, 1.1.14, and 1.15 (all s, together 6 H); 2.64, 2.71, 2.88, 2.90, 3.06, 3.18 (all s, together 9 H); 4.76 and 5.00 (both br, together 1 H); 4.95 and 5.09 (both dd, together 1 H); 6.08 and 6.28 (both d, together 1 H); 6.83 and 7.00 (both m, together 1 H).

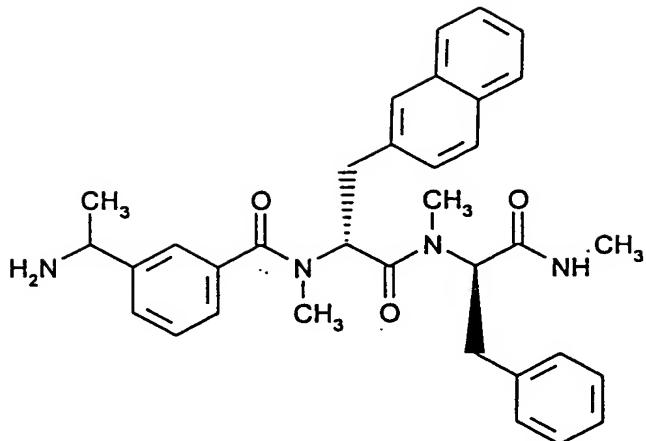
²⁰ MS: 579.0 [M+H]⁺.

HPLC: R_t = 31.98 min (A1).
R_t = 27.53 min (B1).

²⁵ For biological testing the title compound was transferred into its acetate by lyophilization from 40 ml 0.5 M aqueous acetic acid.

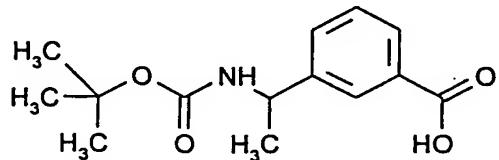
Example 34

³⁰ 3-(1-Aminoethyl)benzoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



5

3-(1-(N-tertbutoxycarbonyl)aminoethyl)benzoic acid:



Ammonium acetate (10.6 g, 138 mmol) was evaporated from dry ethanol
 10 (100 mL), and redissolved in dry methanol (100 mL) over molecular sieves
 (3Å, 3 g). 3-Acetylbenzonitrile (2.0 g, 13.8 mmol) was added. After 30
 minutes at room temperature sodium cyanoborohydride (0.87 g, 138 mmol)
 was added and the reaction mixture was stirred for 18 hours. The reaction
 mixture was concentrated in vacuo and redissolved in water (100 mL).
 15 Concentrated hydrochloric acid was added until pH 2, and the aqueous
 solution was extracted with ethyl acetate (2 x 100 mL). The aqueous phase
 was adjusted to pH 11 with solid potassium hydroxide, and extracted with
 dichloromethane (2 x 100 mL). The combined organic phases were dried
 (magnesium sulfate) and concentrated in vacuo. A concentrated solution of
 20 hydrogen chloride in ethyl acetate added (100 mL) was, and the solution
 was concentrated in vacuo. The residue was dissolved in ethanol (25 mL)

and sulphuric acid (9N, 25 mL) was added. After 16 hours at room temperature and 2 hours at reflux temperature the ethanol was removed by evaporation in vacuo and the residual aqueous mixture was adjusted to pH > 8 using solid potassium hydroxide. Ditertbutyldicarbonate (2.0 g) dissolved in tetrahydrofuran (100 mL) was added at 0°C. After 18 hours at room temperature the reaction mixture was concentrated in vacuo and redissolved in water (100 mL). Solid citric acid was added until pH 5. The reaction mixture was extracted with dichloromethane (2 x 100 mL), and the combined organic phases was dried (magnesium sulfate) and concentrated in vacuo.

10 The residue was purified by column chromatography on silica gel (3 x 40 cm) using ethanol and dichloromethane (1:9) as eluent to give 1.1 g of 3-(1-(N-tertbutoxycarbonyl)aminoethyl)benzoic acid.

15 3-(1-(N-tert-Butyloxycarbonyl)aminoethyl)benzoic acid (132 mg, 0.50 mmol), 1-hydroxy-7-azabenzotriazole (68 mg, 0.50 mmol) and 1-ethyl-3(3-dimethylaminopropyl)carbodiimide hydrochloride (96 mg, 0.50 mmol) were dissolved in N,N-dimethylformamide(3 mL) and stirred for 15 min.
(2R)-N-Methyl-N-((1R)-2-phenyl)-1-(methylcarbamoyl)ethyl)-2-methylamino-

20 3-(2-naphtyl)propionamide (100 mg; 0.25 mmol) dissolved in dichloromethane (6 mL) was added followed by addition of diisopropylethylamine (0,085 mL, 0.50 mmol) and the mixture was stirred for 20 hours.

The reaction mixture was evaporated in a stream of nitrogen and the residue

25 was dissolved in ethyl acetate (25 mL). The mixture was washed with aqueous sodium hydrogen carbonate (2 x 25 mL, 5%) and aqueous potassium hydrogen sulfate (25 mL, 5%). The organic phase was dried (sodium sulfate) and evaporated in vacuo. The residue was dissolved in dichloromethane (2.5 mL), cooled to 0-4° C and treated with trifluoroacetic acid (2.5 mL) for 10 minutes at 0-4° C. The volatiles were removed with a stream of nitrogen an the oily residue was dissolved in 0,1 % triflouroacetic acid in acetonitrile and water (7:3, 10 mL) and diluted with water (290 mL).

This solution was submitted to semipreparative HPLC purification using a 25x200 mm C18 column and using a linear gradient of 25-40% acetonitrile in water containing 0.1M ammonium sulfate (pH 2.5). The product was purified in three runs and after ion exchange on a Waters Seppak C18 the effluent was lyophilised to give the title compound.

PD-MS: Calculated 551.7 (M+1); Found 551.3 (M+1)

HPLC: $R_t = 31.8$ min (Method A1)

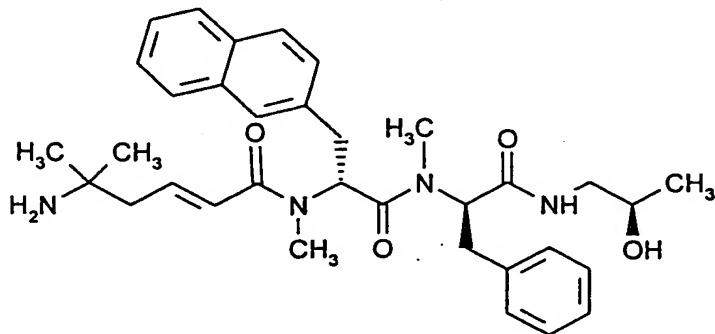
$R_t = 33.93$ min (Method B1)

10

Example 35

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2R)-2-hydroxypropylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)

15 methylamide:



20 The title compound was prepared analogously to example 1.

$^1\text{H-NMR}$ (CDCl_3): (selected peaks for major rotamer) d 1.09 (d, 3H); 1.19 (s, 6H); 2.97 (s, 3H); 2.99 (s, 3H); 5.15 (dd, 1H); 5.53 (dd, 1H); 6.12 (d, 1H)

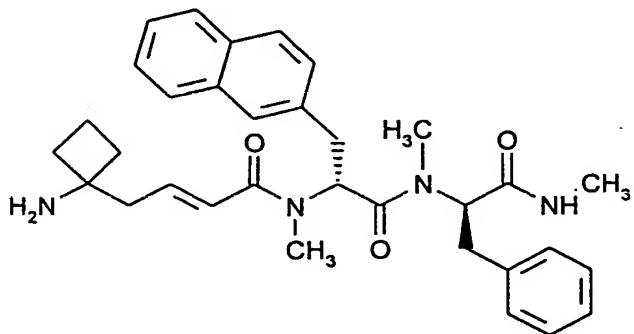
25 HPLC : $r_t = 31.8$ min. (A1)

PDMS : m/z 573.7 (M+H)⁺

5 Example 36

(4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-(((1R)-1-(1-methylcarbamoyl-2-phenylethyl)methylcarbamoyl)-2-(naphthyl)ethyl)methylamid
e:

10



The title compound was prepared analogously to example 1. (4-
15 (1-Aminocyclobutyl)but-2-enoic acid was prepared as in R. Graf, Org. Synth. 46,
51 (1966) and example 1.

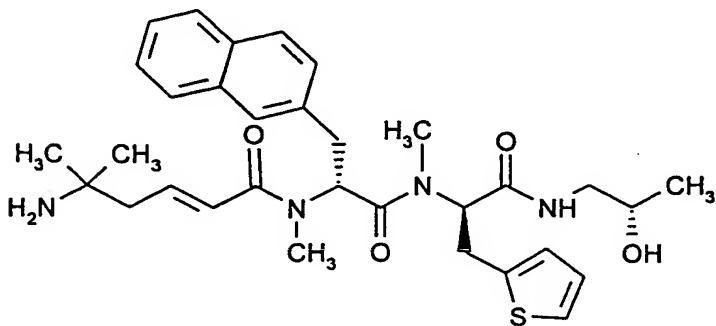
¹H-NMR (CDCl₃): (selected peaks for major rotamer) d 2.26 (s, 3H); 2.98 (s, 3H);
3.00 (s, 3H); 5.15 (dd, 1H); 5.57 (dd, 1H); 6.11 (d, 1H).

20

HPLC : r_t= 32.2 min. (A1)

Example 37

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-
 5 2-hydroxypropylcarbamoyl)-2-(2-thienyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.



10

This compound was prepared analogously to example 1.

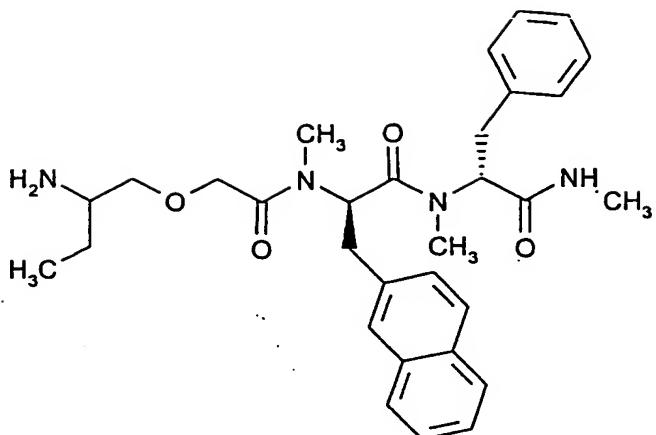
¹H-NMR (CDCl₃): (selected peaks for major rotamer) d 1.10 (d, 3H); 1.14 (s, 3H);
 1.15 (s, 3H); 2.18 (d, 2H); 2.95 (s, 3H); 3.05 (s, 3H); 5.28 (dd, 1H); 5.72 (dd, 1H);
 15 6.07 (d, 1H).

HPLC : r_f = 30.4 min. (A1)

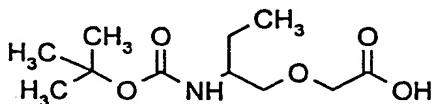
Example 38

20

(2R)-2-(N-[(2R)-2-(N-[(2-Aminobutoxy)acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide:



(2-(tert-Butoxycarbonylamino)butoxy)acetic acid :



5 To a solution of (1-(hydroxymethyl)propyl)carbamic acid tert-butylester (7.2 g, 39 mmol) in 1,2-dichloroethane (500 ml) rhodium(II)acetate (180 mg) was added and the mixture was heated to 80 °C. Ethyldiazoacetate (6.0 ml, 57 mmol) in 1,2-dichloroethane (180 ml) was added over a period of 60 min and the mixture was

10 heated at 80 °C for 6 hours. Then another portion of ethyldiazoacetate (2.0 ml, 19 mmol) in 1,2-dichloroethane (40 ml) was added and the mixture was refluxed for 7 hours. The mixture was cooled to room temperature and washed with sodium bicarbonate (2 x 100 ml) and brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (300 g)

15 with pentane/ethyl acetate 7:3 as eluent to give 4.3 g of (2-(tert-butoxycarbonylamino)butoxy)acetic acid ethylester. The product was dissolved in of 1 M lithium hydroxide in water/methanol 1:3 (40 ml) and stirred at room temperature for 4 hours. The mixture was concentrated in vacuo and water (100 mL) was added and the solution was washed with ether (20 mL). The aqueous phase was acidified

20 to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (200 ml), dried over magnesium sulfate and concentrated in vacuo to give 2.46 g of (2-(tert-butoxycarbonylamino)butoxy)acetic acid.

¹H-NMR (CDCl₃): δ 0.95 (t, 3H) 1.45 (s, 9H) 1.60 (m, 3H) 3.55 (m, 2H) 4.10 (s, 2H)

5 To a solution of (2-(tert-butoxycarbonylamino)butoxy)acetic acid (1.1 g, 4.5 mmol) in dichloromethane (20 ml) were added 1-hydroxy-7-azabenzotriazole (612 mg, 4.5 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (9.5 mg, 5.0 mmol) and the mixture was stirred for 30 min. (2R)-N-methyl-2-methylamino-N-((1R)-1-methyl-carbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (605 mg, 1.5 mmol) in dichloromethane (10 ml) was added followed by diisopropylethylamine (0.33 ml, 2.0 mmol) and the mixture was stirred for 2 hours at room temperature.

10 The mixture was washed with water (10 ml), saturated aqueous sodium bicarbonate (10 ml), water (2 × 10 ml), brine (10 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (40 g) with ethyl acetate/heptane 4:1 to give 766 mg of (1-[{N-methyl-N-((1R)-1-[N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl]-carbamoyl]-2-(2-naphthyl)ethyl]carbamoyl}methoxymethyl]-propyl)carbamic acid tert-butylester. The obtained product was taken up in 50% trifluoroacetic acid in dichloromethane (5 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8

15 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo to give (2R)-2-(N-[(2R)-2-(N-[{2-aminobutoxy}acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide as an oil. The product was

20 redissolved in water (30 ml) and acetic acid (2 ml) was added and the mixture was lyophilized to give 645 mg of the acetate salt of the title compound as an amorphous powder.

25

LC-MS : 533.0 (M+H)⁺

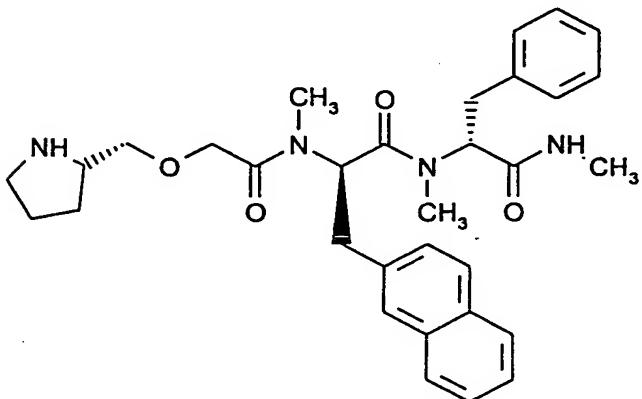
30 HPLC: R_t = 31.1 (Method A1)

¹H-NMR (DMSO) (selected peaks): d 0.6-0.8 (m, 3H) 2.65 (d, 3H) 2.75 (s, 3H) 5.35 (dd, 1H) 5.65 (dd, 1H) 7.1-7.9 (arom, 12H)

Example 39

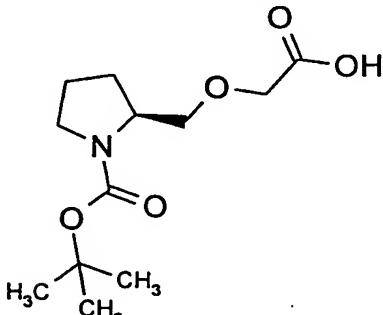
5

(2R)-N-Methyl-2-(N-methyl-N-((2R)-2-(N-methyl-N-(((2S)-pyrrolidin-2-yl)methoxy)acetyl)amino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionamide



10

(2S)-2-((Carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester



To a solution of N-t-butyloxycarbonyl-(S)-prolinol (5.0 g, 25 mmol) in 1,2-dichloroethane (500 ml) rhodium(II)acetate (180 mg) was added and the mixture was heated to 80 °C. Ethyldiazoacetate (3.9 ml, 37 mmol) in 1,2-dichloroethane (180 ml) was added over a period of 90 min and the mixture was heated at 80 °C for 3 hours. Then another portion of ethyldiazoacetate (1.3 ml, 12 mmol) in 1,2-dichloroethane (40 ml) was added and the mixture was refluxed for 6 hours. The mixture was cooled to room temperature and washed with saturated sodium

bicarbonate (2 x 100 ml) and brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (300 g) with petrol ether/ethyl acetate 4:1 as eluent to give 4.7 g of (2S)-2-(((ethoxycarbonyl)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester. The obtained product was taken up in 50 ml of 1 M lithium hydroxide in water/methanol 1:3 and stirred at room temperature overnight. The mixture was concentrated in vacuo, water (20 mL) was added and washed with ether (20 mL). The aqueous phase was acidified to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (200 ml), dried over magnesium sulfate and concentrated in vacuo to give 3.6 g of (2S)-2-((carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester.

¹H-NMR (CDCl₃): δ 1.45 (2, 9H) 1.90 (m, 4H) 3.55 (t, 2H) 3.60 (m, 3H) 4.10 (s, 2H) 10.6 (s, 1H)

15

To a solution of (2S)-2-((carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester (1.2 g, 4.5 mmol) in dichloromethane (20 ml) were added 1-hydroxy-7-azabenzotriazole (612 mg, 4.5 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (950 mg, 4.95 mmol) and the mixture was stirred for 30 min. (2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (605 mg, 1.5 mmol) in dichloromethane (10 mL) was added followed by diisopropylethylamine (0.33 ml, 2.0 mmol) and the mixture was stirred for 2 hours at room temperature. The mixture was washed with water (10 ml), aqueous sodium bicarbonate (10 ml), water (2 x 10 ml), brine (10 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (40 g) with ethyl acetate/heptane 4:1 to give 760 mg of (2S)-2-([N-methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl)methoxymethyl)pyrrolidine-1-carboxylic acid tert-butylester. The obtained product was taken up in 50% trifluoroacetic acid in methylene chloride (5 ml) and stirred for 10 min. Then saturated sodium

bicarbonate was added until pH 8 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The product was redissolved in water (30 ml) and acetic acid (2 ml) was added and the mixture was lyophilized to give 720 mg of the acetate salt of the title compound as an amorphous powder.

¹H-NMR (DMSO) (selected peaks): δ 0.75 (m, 1H) 1.35 (m, 1H) 1.6 (m, 1H) 1.7 (m, 1H) 2.65 (d, 3H) 2.75 (d, 3H) 3.95 (d, 2H) 5.35 (dd, 1H) 5.55 (dd, 1H)

10

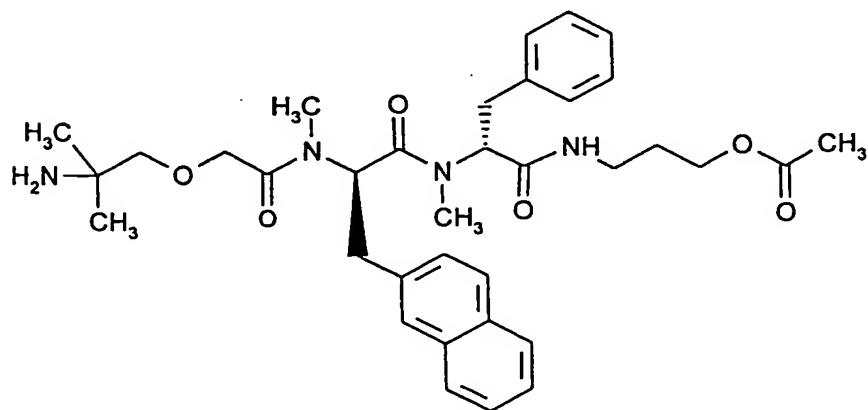
LC-MS : 544.8 (M+H)⁺

HPLC: R_t = 31.1 (Method A1)

Example 40

15

3-((2R)-2-(N-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate



20

To a solution of (2-t-butoxycarbonylamino-2-methylpropoxy) acetic acid (504 mg, 2.0 mmol) in dichloromethane (10 ml) were added 1-hydroxy-7-azabenzotriazole (278 mg, 2.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (429 mg, 2.3 mmol) and the mixture was stirred for 30 min. 3-((2R)-2-(N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-propyl acetate (500 mg, 1.0 mmol) in dichloromethane (10 mL) was added followed by diisopropylethylamine (0.23 ml, 1.32 mmol) and the mixture was stirred overnight at room temperature. The mixture was washed with water (10 ml), aqueous sodium bicarbonate (10 ml), water (2 x 10 ml), brine (10 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (60 g) with ethyl acetate/heptane 4:1 to give 623 mg of 3-((2R)-2-(N-((2R)-2-(N-((2-(tert-butoxycarbonylamino)-2-methylpropoxy) acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-propyl acetate as an oil. The obtained product was taken up in 50% trifluoroacetic acid in dichloromethane (3 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The product was redissolved in water (30 ml) and the mixture was lyophilized to give 434 mg of the title compound as an amorphous powder.

20 $^1\text{H-NMR}$ (CDCl_3) (selected peaks): d 1.1 (s, 3H) 1.2 (s, 3H) 2.0 (s, 3H) 2.15 (s, 3H) 5.7 (m, 2H) 5.25 (m, 1H)

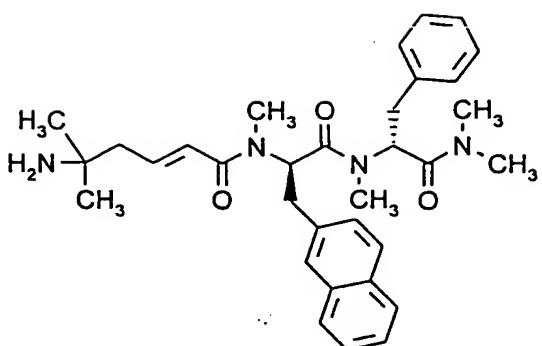
LC-MS : 619.6 ($\text{M}+\text{H})^+$

HPLC: R_t = 33.2 (Method A1)

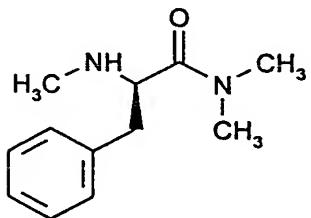
25

Example 41

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



5 (2R)-N,N-Dimethyl-2-methylamino-3-phenylpropionamide



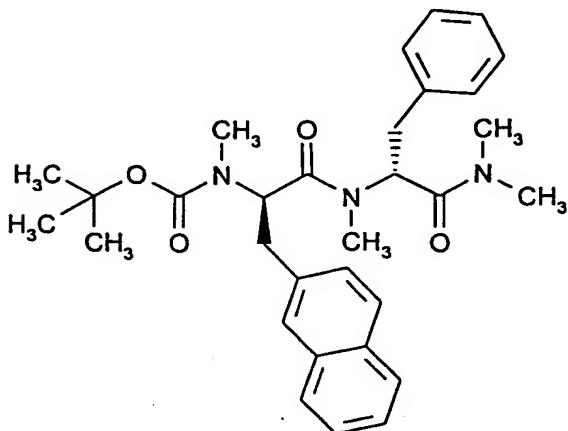
To a solution of (2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropionic acid (10.0 g, 36.0 mmol) in dichloromethane (200 ml) was added 1-hydroxy-7-azabenzotriazole (6.8 g, 50.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10.0 g, 55.0 mmol) and the mixture was stirred for 30 min. Then dimethylamine hydrochloride (4.1 g, 50.0 mmol) in dichloromethane (100 ml) and diisopropylethylamine (19.0 ml, 110 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (100 ml) aqueous sodium bicarbonate (100 ml), water (2 x 100 ml), brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with dichloromethane/methanol 20:1 to give 6.3 g of (2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionic acid N,N-dimethylamide. The product was dissolved in 50% trifluoroacetic acid in dichloromethane (5 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo to give 4.58 mg of (2R)-N,N-

dimethyl-2-methylamino-3-phenylpropionamide.

¹H-NMR (CDCl₃): d 2.3 (s, 3H) 2.7 (s, 3H) 2.9 (s, 3H) 2.8-3.4 (m, 2H) 4.45 (m, 1H)
7.1-7.3 (m, 5H)

5

N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester



To a solution of (2R)-(N-tert-butoxycarbonyl-N- methylamino)-3-

10 (2-naphthyl)propionic acid (8.78 g, 26.6 mmol) in dichloromethane (30 ml) were added 1-hydroxy-7-azabenzotriazole (3.62 g, 26.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.54 mg, 28.9 mmol) and the mixture was stirred for 30 min. Then (2R)-N,N-dimethyl-2-methylamino-3-phenylpropionamide (4.58 g, 22.2 mmol) in dichloromethane (15 ml) and
15 diisopropylethylamine (4.94 ml, 28.9 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (20 ml), aqueous sodium bicarbonate (20 ml), water (2 x 20 ml), brine (20 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with ethyl acetate/heptane 1:4 to give 6.64 g of
20 N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃) (selected peaks for rotamers): d 1.1 and 1.4 (two s, 9H) 2.2, 2.3, 2.7 and 2.8 (four s, 6H) 2.35 and 2.6 (two s, 3H) 2.9 and 3.0 (two s, 3H)

A solution of N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester (6.6 g, 12.8 mmol) in 50% trifluoroacetic acid/dichloromethane (15 ml) was stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 20 ml) and the combined organic phases were washed with brine (10 ml), dried over magnesium sulfate and concentrated in vacuo to give 4.2 g of (2R)-N-((1R)-1-dimethylcarbamoyl-2-phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

¹H-NMR (CDCl₃): δ 2.7 (s, 3H) 2.75 (s, 3H) 2.85 (s, 3H) 2.9-3.15 (m, 4H) 3.7 (t, 1H) 5.8 (t, 1H) 7.1-7.8 (arom, 12H)

15 To a solution of (2E)-5-(tert-butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.5 g, 2.1 mmol) in dichloromethane (5 ml) was added trifluoroacetic acid (5 ml) and stirred for 60 min and concentrated in vacuo. Then a 10% aqueous solution of sodium carbonate (30 ml) and dioxane (30 ml) were added followed by 9H-fluorenylmethyl-succinimidyl carbonate (0.67 g, 2.1 mmol) and stirred overnight.

20 The mixture was washed with petrol ether (2 x 20 ml) and the aqueous layer was acidified with 4N sulphuric acid (pH~3) and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with 1N sulfuric acid, water (4 x 20 ml), brine (20 ml), dried (Magnesiumsulfate) and concentrated in vacuo. The obtained product was precipitated from dichloromethane/ether and filtered to give 280 mg of

25 (2E)-5-(((9H-flouren-9-yl)methoxy)carbonylamino)-5-methyl-hex-2-enoic acid, which was used without further purification.

To a solution of (2E)-5-(((9H-flouren-9-yl)methoxy)- carbonylamino)-5-methylhex-2-enoic acid (280 mg, 0.77 mmol) in dichloromethane (5 ml) were added 1-hydroxy-7-azabenzotriazole (126 mg, 0.92 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (207 mg, 1.08 mmol) and the mixture was stirred for 30 min. Then 2R)-N-((1R)-1-dimethylcarbamoyl-2-

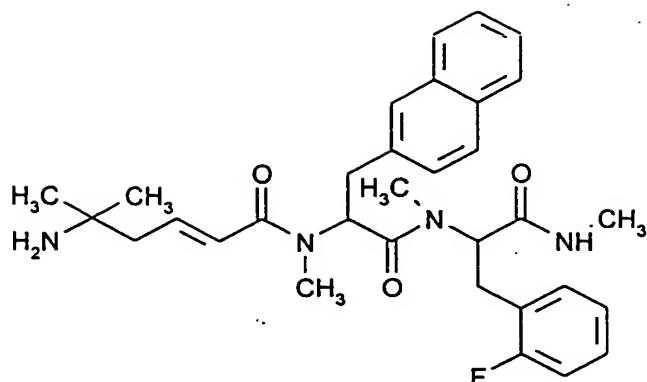
B
O
D
D
E
C
H
E
R
I
C
H
E
R

phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (386 mg, 0.92 mmol) in dichloromethane (5 ml) and diisopropylethylamine (0.17 ml, 1.00 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (20 ml), saturated aqueous sodium bicarbonate (20 ml), water (2 x 20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (400 g) with ethyl acetate/heptan 1:1 to give 401 mg of ((3E)-4-(N-((1R)-1-(N-((1R)-1-dimethylcarbamoyl-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid 9H-flouren-9-ylmethyl ester. The obtained product was dissolved in 20% piperidine in dimethylformamide (10 ml) and stirred for 30 min. The mixture was chromatographed on silica (20 g) with dichloromethane/methanol/ammonia 89:10:1 to give 228 mg of (2E)-5-amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide as an oil. The product was redissolved in water (30 ml) and acetic acid (2 ml) was added and the mixture was lyophilized to give 645 mg of the acetate salt of the title compound as an amorphous powder.

LC-MS : 543.0 (M+H)⁺
 20 HPLC: R_t = 32.9 (Method A1)

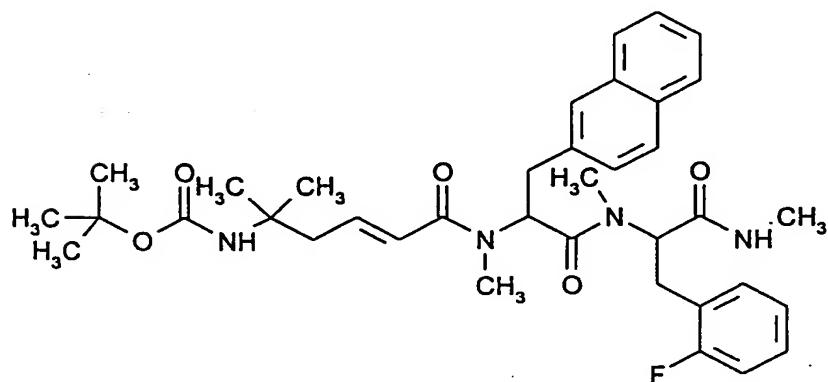
¹H-NMR (DMSO) (selected peaks): d 1.0 (s, 6H) 1.8 (s, 6H) 2.4 (s, 3H) 2.7 (s, 3H) 2.8 (s, 3H)

25 Example 42
 5-Amino-5-methyl-hex-2-enoic acid
 (1-[{2-(2-fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl}-2-(2-naphthyl)ethyl)methylamide.



{4-[(1-[(2-(2-Fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl]-2-(2-naphthyl)ethyl)methylcarbamoyl]-1,1-dimethyl-but-3-enyl}carbamic acid tert-butyl ester.

10



15 (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.19 g; 0.783 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxy-7-azabenzotriazole (0.12 g; 0.861 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.900 mmol) was

added and the reaction mixture was stirred 15 min at room temperature.

N-[2-(2-Fluorophenyl)-1-methylcarbamoylethyl]-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.33 g; 0.783 mmol) and diisopropyl ethylamine (0.15 ml; 0.861 mmol) was added and the reaction mixture was stirred 12 hours at room

5 temperature.

Methylene chloride (50 ml) was added and the reaction mixture was washed with water (50 ml), sodium hydrogen sulfate (10 %; 50 ml), sodium hydrogen carbonate (sat; 50 ml), water (50 ml) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.366 g of

10 {4-[(1-[2-(2-Fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl]-2-(2-naphthyl)ethyl)methylcarbamoyl]-1,1-dimethyl-but-3-enyl}carbamic acid tert-butyl ester.

{4-[(1-[2-(2-Fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamoyl]-1,1-dimethyl-but-3-enyl}carbamic acid tert-butyl ester (0.36

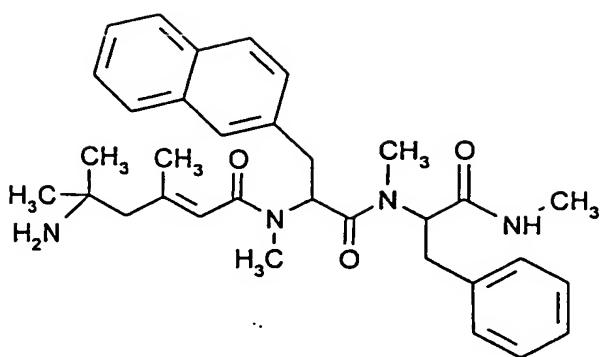
15 g; 0.557 mmol) was dissolved in methylene chloride (3 ml). Trifluoro acetic acid (3 ml) was added and the reaction mixture was stirred 5 min at room temperature. Methylene chloride (25 ml), sodium hydrogen carbonate/sodium carbonate (3 ml) and sodium hydrogen carbonate (s) was added until pH=8. The organic phase was dried (magnesium sulfate) and the solvent was removed in vacuo. The residue was

20 lyophilised to afford 0.237 g of the title compound.

Example 43

25 (2Z)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



5

(Z)(1,1,3-trimethyl-4-(methyl-(1-methyl carbamoyl-2-phenyl ethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester(0.009 g ; 0.014 mmol.) was dissolved in methylene chloride (0.12 mL) and trifluoro acetic acid (0.08 mL) was added. The reaction mixture was stirred 5 min at room temperature. Water (0.100 mL) was added. The solvent was removed in vacuo to afford 0.007 g (2Z)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide ; trifluoro acetic acid salt.

15

ESMS : $M_w = 542.4$

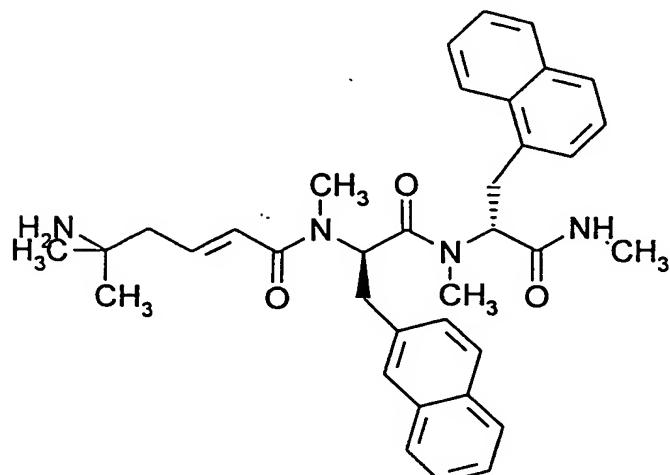
20

HPLC : $R_t = 34.82$

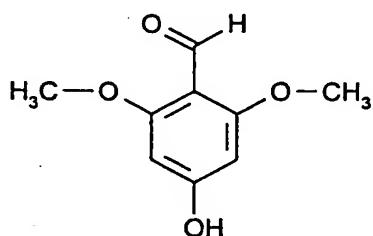
Example 44

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-

naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)amide:



5 4-Formyl-3,5-dimethoxyphenol:

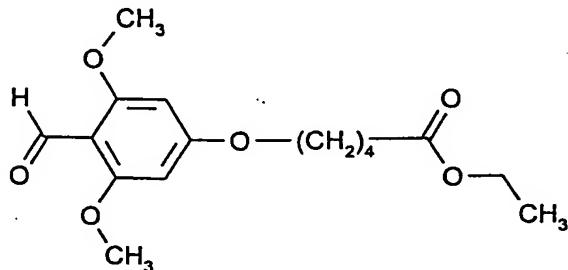


To a solution of 3,5-dimethoxyphenol (50 g, 320 mmol) in phosphorous oxychloride (60 mL, 650 mmol) at 0 °C was added dimethylformamide (37 mL, 490 mmol) over a period of 30 min and the mixture was warmed to room temperature and stirred overnight. The mixture was added to icewater (600 mL) and the mixture was washed with ether (3 x 200 mL). Then an 32 % aqueous solution of sodium hydroxide was added until pH was 5.5 and the compound precipitated. The precipitate was separated and washed with water (100 mL) and ether (100 mL) and dried in vacuo. The precipitate was recrystallized from ethanol (600 mL) to give 22.6 g of 4-formyl-3,5-dimethoxyphenol.

bp. 224-226 °C

¹H-NMR (DMSO): d 3.75 (s, 6H) 6.1 (s, 2H) 10.1 (s, 1H)

Ethyl 5-(4-formyl-3,5-dimethoxyphenoxy)valerate:



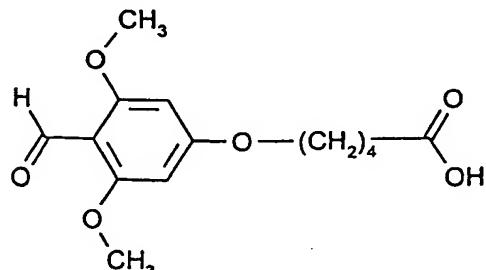
5

To a suspension of 4-formyl-3,5-dimethoxyphenol (22.6 g, 124 mmol) and potassium tert-butoxide (15.3 g, 136 mmol) in dimethylformamide (125 mL) was added ethyl 5-bromovalerate (28.5 g, 136 mmol) in dimethylformamide (125 mL) over a period of 20 min. The mixture was heated at 110 °C for 6 h
10 and concentrated in vacuo. To the obtained product was added ethyl acetate (400 mL) and the mixture was filtered. The filtrate was washed with water (100 mL), 1 N sodium hydroxide (2 x 50 mL), and brine (3 x 100 mL), dried (magnesium sulfate), and concentrated in vacuo to 37 g of ethyl 5-(4-formyl-3,5-dimethoxyphenoxy)valerate.

15

¹H-NMR (CDCl₃): d 1.25 (t, 3H) 1.85 (m, 4H) 2.4 (m, 2H) 3.9 (s, 6H)
4.05 (t, 2H) 4.15 (q, 2H) 6.1 (s, 2H) 10.3 (1H)

5-(4-Formyl-3,5-dimethoxyphenoxy)valeric acid:



20

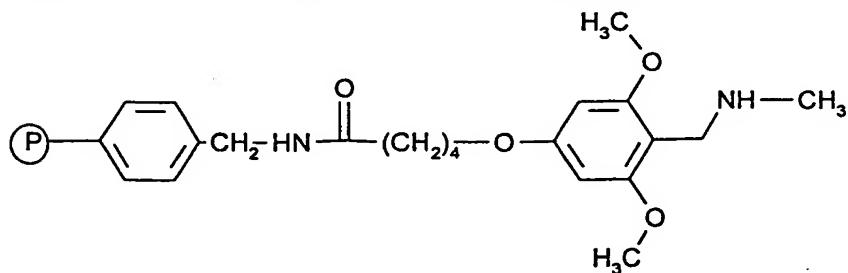
To a solution of ethyl 5-(4-formyl-3,5-dimethoxyphenoxy) valerate (37 g, 119 mmol) in methanol (200 mL) was added 4 N sodium hydroxide (200 mL) and

the mixture was stirred for 2 h. The methanol was removed in vacuo, water (100 mL) was added and the mixture was washed with ethyl acetate (100 mL) and dichloromethane (2 x 100 mL). The aqueous layer was acidified with 12 N hydrochloric acid until pH~3 and extracted with ethyl acetate (2 x 5 200 mL). The combined organic layers were washed with brine (2 x 50 mL), dried (magnesium sulfate) and concentrated in vacuo. The obtained product was recrystallized from ethanol to give 26 g of 5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid.

10 bp. 134-136 °C

¹H-NMR (CDCl₃): d 1.85 (m, 4H), 2.45 (m, 2H) 3.85 (s, 6H) 4.05 (m, 2H) 6.05 (s, 2H) 10.3 (s, 1H)

15 N-Methyl-PAL-Resin for Solid-Phase Synthesis (PAL defined as in F. Albericio et al., J. Org. Chem., 55 (1990) pp. 3730-3743) :



Aminomethylated polystyrene resin (10 g, 7.8 mmol, purchased from Bachem AG, # D-1005) and 1-hydroxybenzotriazole hydrate(1 g, 6.6 mmol) 20 in dimethylformamide (100 mL) were shaken overnight. The resin was filtered and the resin was repeatedly swelled in dichloromethane and dimethylformamide until a homogeneous resin was obtained. The resin was washed with 5% diisopropylethylamine in dimethylformamide (2 x 100 mL) and dimethylformamide (100 mL), successively. A solution of 5-(4-formyl-25 3,5-dimethoxyphenoxy)valeric acid (6.6 g, 23 mmol), 1-hydroxybenzotriazole hydrate (3.5 g, 23 mmol) and diisopropylcarbodiimide (3.6 mL, 23 mmol) in dimethylformamide/dichloromethane 2:1 (50 mL) was added. After 5 h at

room temperature the resin was filtered and washed with dimethylformamide (3 x 100 mL), dichloromethane (3 x 50 mL) and dichloromethane/methanol 1:1 (3 x 100 mL) and dried with a stream of nitrogen.

To the resin in dimethylformamide (50 mL) were added 5% acetic acid in

5 dimethylformamide (50 mL) and 40 % methylamine in methanol (3.0 mL, 39 mmol) and the mixture was shaken for 20 min. Sodium triacetoxyborohydride (8.3 g, 39 mmol) was added and the mixture was shaken overnight. The mixture was filtered and the resin was washed with dimethylformamide (3 x 50 mL), dichloromethane (3 x 50 mL),

10 dichloromethane/methanol 1:1 (3 x 50 mL), ether (3 x 50 mL) and dried with a stream of nitrogen to give 10 g of N-Methyl-PAL-Resin (loading: 0.35-0.45 mmol/g based on N-analysis).

Calc: N 1.82 %

15 Found: N 1.47 %

The N-Methyl-PAL-Resin (450 mg) was washed with 5 % diisopropylethylamine in dichloromethane (2 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (3 x 2 mL) and then swelled in

20 dimethylformamide (7 mL). Then (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid (163 mg, 0.36 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.36 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol) in dimethylformamide (1 ml) and diisopropylethylamine (123 mL, 0.72 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then (2R)-2-(N-((9H-fluoren-9-

yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (163 mg, 0.36 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.36 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (123 mL, 0.72 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then (2E)-5-(N-tert-butoxycarbonylamino)-5-methylhex-2-enoic acid (88 mg, 0.36 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.36 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (123 mL, 0.72 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). The resin was cooled to 0 °C and 50 % trifluoroacetic acid in dichloromethane (4 mL) was added and the mixture was shaken for 10 min at 0 °C. The resin was filtered and washed with 50 % trifluoroacetic acid in dichloromethane (2 x 0.5 mL) and the combined filtrates were concentrated under a stream of nitrogen. The obtained product was dissolved in acetonitrile/water 1:20 (10 mL) and applied to a C-18 Sep-Pak Classic© cartridge (0.25 g, purchased from Waters™), which had been prewashed with acetonitrile (10 mL) and water (10 mL). Then water/trifluoroacetic acid 99.9:0.1 (5 mL), followed by water/acetonitrile/trifluoroacetic acid 89.9:10:0.1 (4 mL) was run through the Sep-Pak© and the filtrate was discarded. Then the Sep-Pak was washed with water/acetonitrile/trifluoroacetic acid 64.9:35:0.1 (4 mL) and the filtrate was

diluted with water (11 mL) and lyophilized to 52 mg of the title product.

HPLC:(A1) R_t = 35.03 min

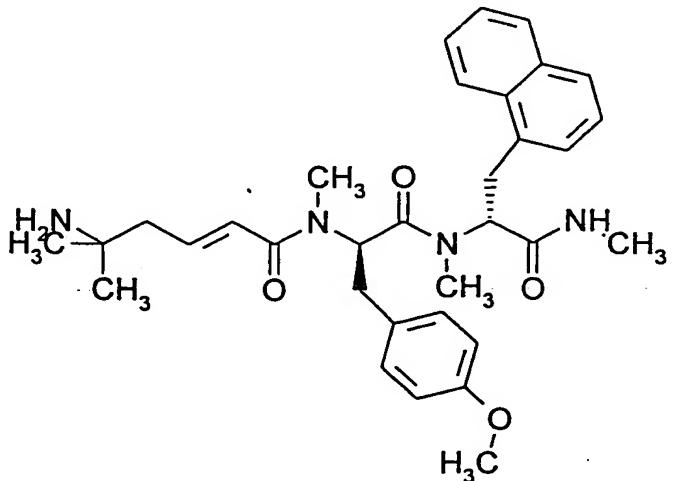
(B1) R_t = 36.93 min

5

LC-MS: 579.0 ($m+1$)⁺

Example 45

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

20

Yield: 44 mg

HPLC:(A1) R_t = 30.22 min

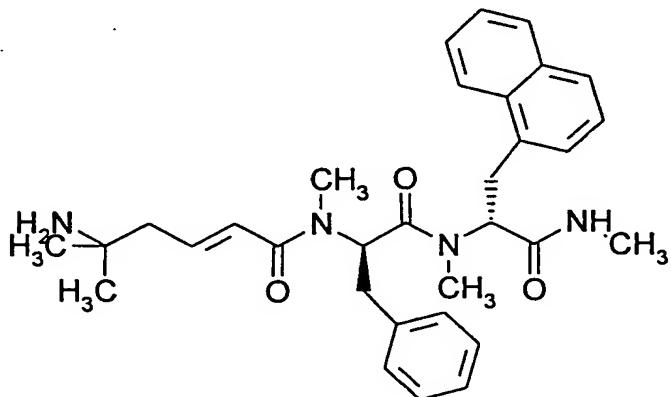
(B1) R_t = 32.10 min

LC-MS: 559.2 ($m+1$)⁺

5

Example 46

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-20 (2-naphthyl)propionic acid.

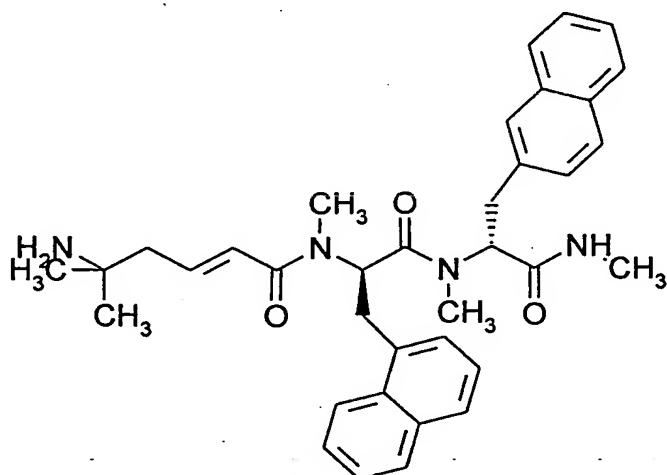
Yield: 38 mg

HPLC:(A1) R_t = 30.68 min

(B1) $R_t = 32.33$ minLC-MS: 529.0 ($m+1$)⁺5 Example 47

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-[(1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl]amide:

10



The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 70 mg

HPLC:(A1) $R_t = 34.52$ min

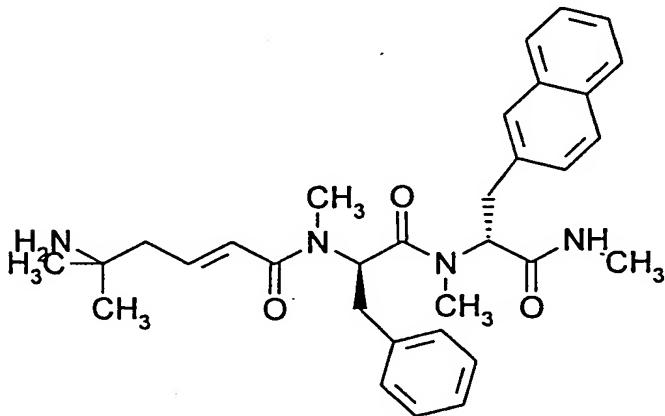
(B1) $R_t = 36.38$ min

LC-MS: 579.0 ($m+1$)⁺

5

Example 48

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



15 The title compound was prepared analogously to example 44 (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid instead of
 20 (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 49 mg

HPLC:(A1) R_t = 30.52 min

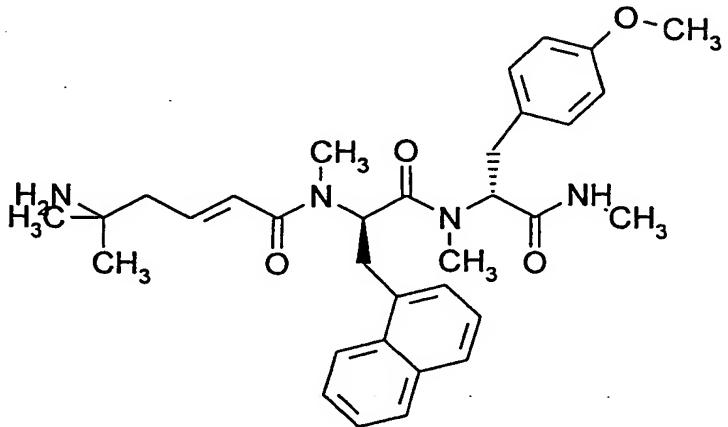
(B1) R_t = 32.03 min

LC-MS: 529.0 ($m+1$)⁺

5

Example 49

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 51 mg

HPLC:(A1) R_t = 30.20 min

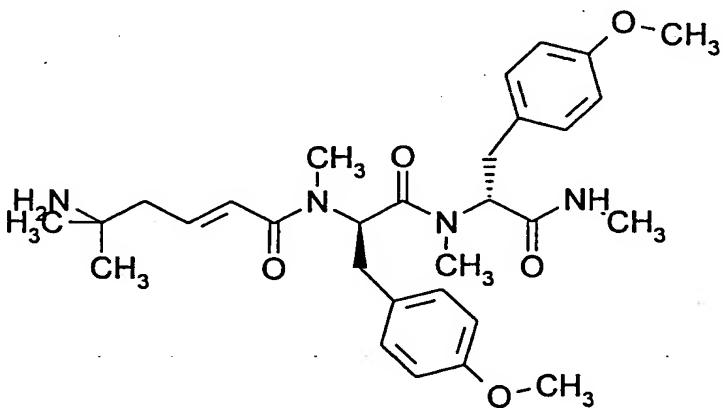
(B1) R_t = 31.70 min

5

LC-MS: 559.2 ($m+1$)⁺

Example 50

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 26 mg

HPLC:(A1) $R_t = 25.75$ min

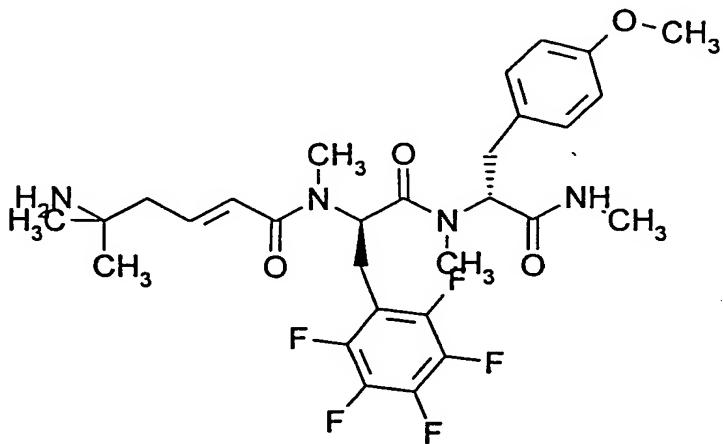
(B1) $R_t = 26.98$ min

5

LC-MS: 539.2 ($m+1$)⁺

Example 51

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 42 mg

HPLC:(A1) $R_t = 31.05$ min

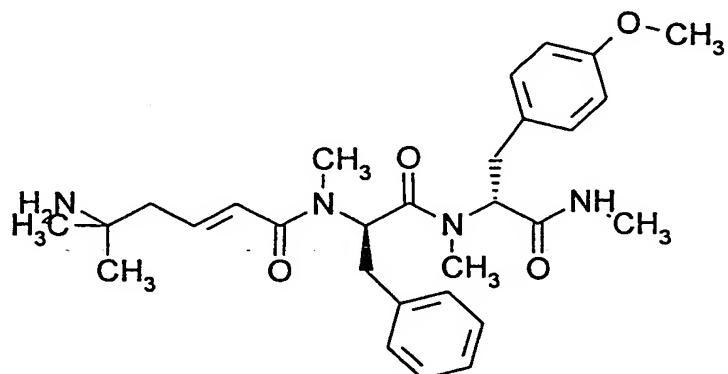
5 (B1) $R_t = 32.00$ min

LC-MS: 599.0 ($m+1$)⁺

Example 52

10

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid
20 instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 31 mg

HPLC:(A1) $R_t = 25.68$ min

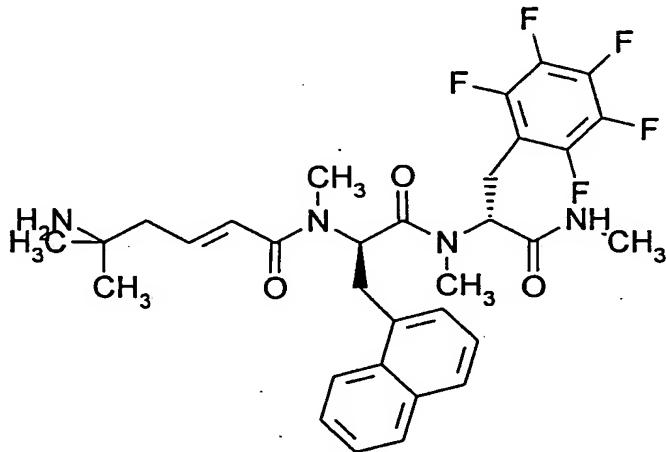
(B1) $R_t = 27.00$ min

5

LC-MS: 509.2 ($m+1$)⁺

Example 53

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl]amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-

yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 38 mg

5 HPLC:(A1) $R_t = 34.88$ min

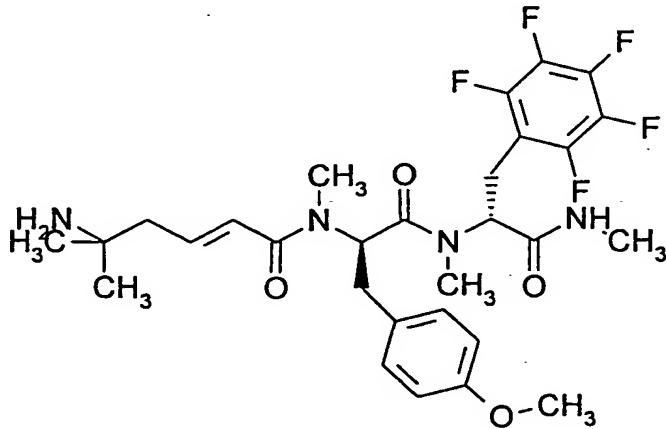
(B1) $R_t = 36.78$ min

LC-MS: 619.0 ($m+1$)⁺

10 Example 54

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl}amide:

15



The title compound was prepared analogously to example 44 with (2R)-2-(N-20 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-

yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 25 mg

5 HPLC:(A1) $R_t = 30.72$ min

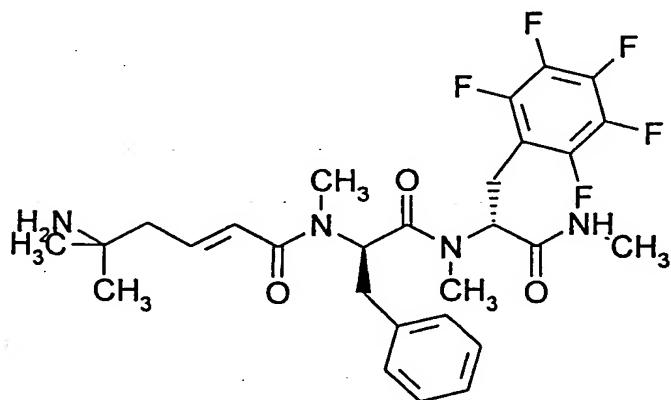
(B1) $R_t = 32.32$ min

LC-MS: 599.0 ($m+1$)¹

10 Example 55

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:

15



The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 30 mg

HPLC:(A1) $R_t = 30.88$ min

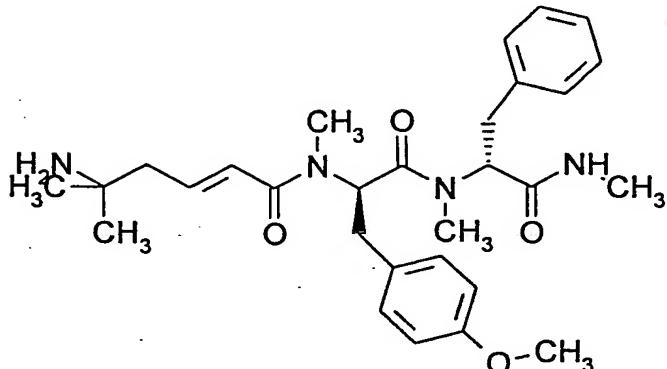
5 (B1) $R_t = 32.55$ min

LC-MS: 569.0 ($m+1$)⁺

Example 56

10

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl]amido:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 25 mg

HPLC:(A1) $R_t = 25.95$ min

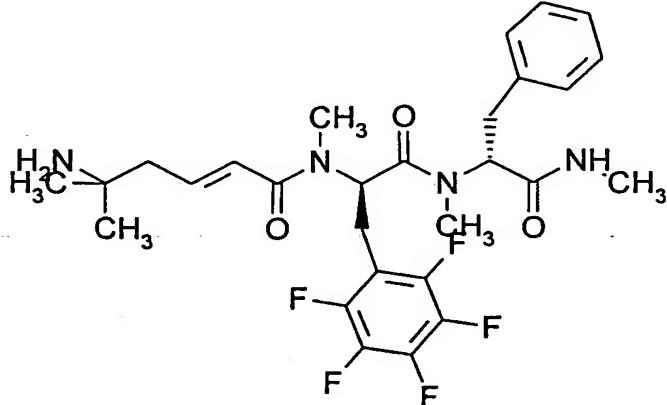
5 (B1) $R_t = 27.23$ min

LC-MS: 509.4 ($m+1$)⁺

Example 57

10

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[{(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-
20 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-

methylamino)-3-(1-naphthyl)propionic acid.

Yield: 35 mg

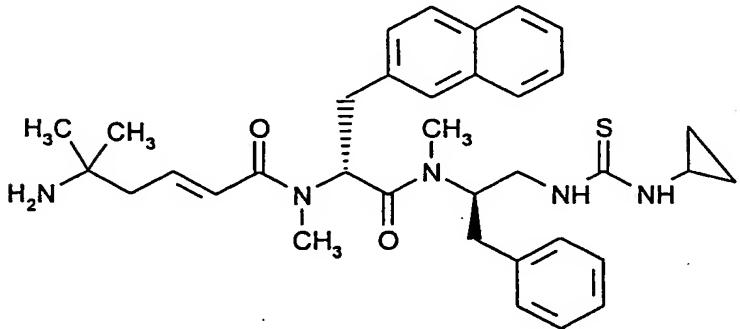
5 HPLC:(A1) R_t = 31.20 min
 (B1) R_t = 32.47 min

LC-MS: 569.0 ($m+1$)¹

10 Example 58

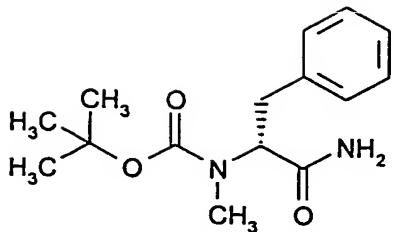
(2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-3-(2-naphthyl)propionamide

15



20

N-((1R)-1-Carbamoyl-2-phenylethyl)-N-methylcarbamic acid tert.-butylester.



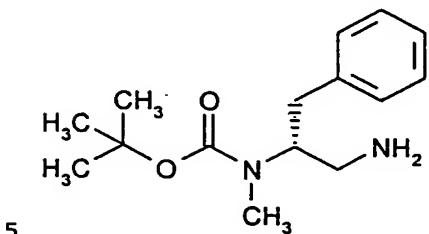
5

A solution of (2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropionic acid (4.00 g, 14.32 mmol) in N,N-dimethylformamide (10 ml) was cooled to 0 °C. Ammonium hydrogen carbonate (5.66 g, 71.60 mmol) was added as a solid. 1-Hydroxybenzotriazole hydrate (1.94 g, 14.32 mmol) and successively N-(3-dimethylaminopropyl)-N'-ethyldiimidoyl hydrochloride (2.75 g; 14.32 mmol) were added. The suspension was stirred for 16 h, while warming up to room temperature. The reaction mixture was diluted with ethyl acetate (150 ml) and extracted with saturated sodium chloride solution/water (200 ml/300 ml). The aqueous phase was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash-chromatography on silica (70 g), using ethyl acetate/heptane as eluent, to give 2.80 g of N-((1R)-1-carbamoyl-2-phenylethyl)-N-methylcarbamic acid tert.-butylester.

20

¹H-NMR (CDCl₃): δ 1.29 and 1.40 (both s, together 9H); 2.74 (s, 3H); 2.95 (m, 1H); 3.37 (m, 1H); 4.75 and 4.96 (both m, together 1H); 5.55, 5.73, 5.95, and 6.17 (all br, together 2 H); 7.05 - 7.40 (m, 5H).

N-((1R)-1-Aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

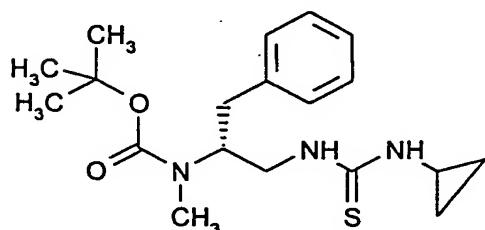


N-((1R)-1-Carbamoyl-2-phenylethyl)-N-methylcarbamic acid tert.-butylester (2.73 g,
 10 9.81 mmol) was dissolved in tetrahydrofuran (10 ml). The solution was cooled to 5 °C. A suspension of sodium borohydride (816 mg, 21.58 mmol) in tetrahydrofuran (10 ml) was added. A solution of iodine (1.24 g, 4.91 mmol) was added dropwise. After the addition was completed, the solution was heated to reflux for 16 h. It was cooled to 5 °C..A 10% solution of ammonium chloride in water (60 ml) was added
 15 dropwise. The solution was warmed to 50 °C for 1 h. It was cooled to room temperature. 1 N sodium hydroxide solution was added until pH 14. It was extracted with tert-butyl methyl ether (4 x 100 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (150 g) using
 20 dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent to give 453 mg of N-((1R)-1-aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃): δ 1.29 and 1.36 (both s, together 9 H); 2.60 - 2.90 (m, 7 H); 4.20
 25 and 4.38 (both br, together 1 H); 7.10 - 7.35 (m, 5 H).

N-((1R)1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamic acid tert-butylester.

5

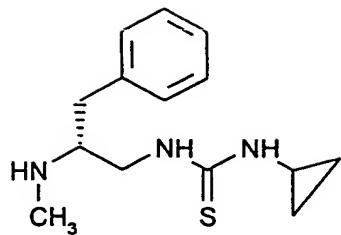


10 At 0 °C, cyclopropylisothiocyanate (0.32 ml) was added to a solution of N-((1R)-1-aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester (410 mg, 1.6 mmol) in dichloromethane (4 ml). The reaction mixture was first stirred at 0 °C for 10 min, and successively for 2.5 h at room temperature. The solvent were removed in vacuo. The crude product was purified by flash chromatography on silica (50 g)

15 using ethyl acetate/heptane as eluent to give 492 mg of N-((1R)1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamic acid tert-butylester.

20 ¹H-NMR (CDCl₃): δ 0.62 (br, 2 H); 1.26 and 1.36 (both s, together 9 H); 2.37 (br, 1 H); 2.60 - 3.00 (m, 5 H); 3.60 (m, 1 H); 3.98 (m, 1 H); 4.60 (m, 1 H); 6.30 and 6.85 (both m, together 2 H); 7.10 - 7.35 (m, 5 H).

N-Cyclopropyl-N'-((2R)-2-methylamino)-3-phenylpropylthiourea.

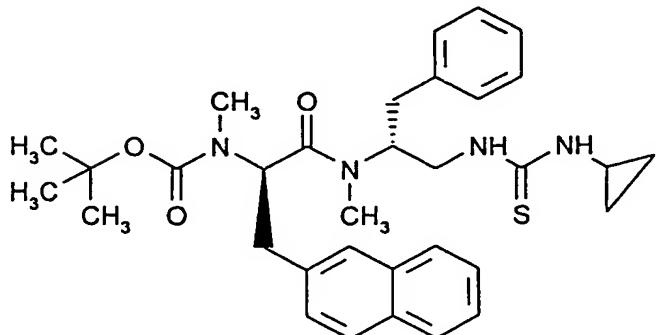


N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamic acid tert-butylester (404 mg, 1.1 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (2 ml) was added. The reaction mixture was stirred for 7 min. The solvents were removed in vacuo. The residue was dissolved in dichloromethane and the solvent was removed in vacuo. This latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (9 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 255 mg of N-cyclopropyl-N'-(2R)-2-methylamino)-3-phenylpropyl)thiourea.

¹H-NMR (CDCl₃): δ 0.64 (br, 2 H); 0.85 (m, 2 H); 2.38 (s, 3 H); 2.45 (m, 1 H); 2.77 (ABX, 2 H); 2.99 (m, 1 H); 3.58 (m, 1 H); 3.74 (m, 1 H); 6.25 (m, 1 H); 7.15 (m, 1 H); 15 7.15 - 7.35 (m, 5 H).

N-((1R)-1-(N-((1R)-1-((3-Cyclopropylthioureido)methyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

20

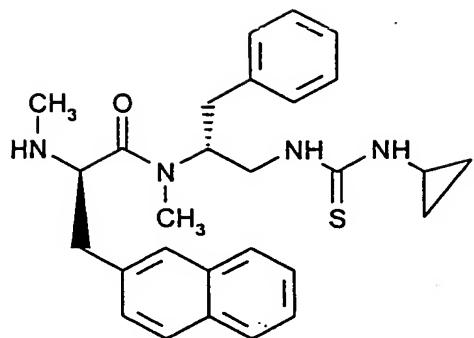


(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (290 mg, 0.88 mmol) was dissolved in dichloromethane (2 ml) and N,N-dimethylformamide (2 ml). 1-Hydroxy-7-azabenzotriazole (120 mg, 0.88 mmol) was added as a solid. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (202 mg, 1.06 mmol) was added. The solution was stirred for 20 min. N-Cyclopropyl-N'-(2R)-2-methylamino)-3-phenylpropyl)thiourea (231 mg, 0.88 mmol) was dissolved in dichloromethane (2 ml) and added. The reaction mixture was stirred for 16 h. It was diluted with ethyl acetate (100 ml) and extracted with 1 N hydrochloric acid (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (45 g) using ethyl acetate/heptane 1:1 as eluent to give 350 mg of N-((1R)-1-(N-((1R)-1-((3-Cyclopropylthioureido)methyl)-2-phenyl-ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃): δ 0.06, 0.19, 0.30, 0.40, 0.55 (all m, together 4 H); 1.25 and 1.33 (both s, together 9 H); 1.41 and 1.60 (both m, together 1 H); 2.12 and 1.27 (both s, together 3 H); 2.70 - 3.00 (m, 6 H); 3.25 (m, 1 H); 3.55 (m, 1 H); 4.00 and 4.15 (both m, together 1 H); 5.02 and 5.37 (both t, together 1 H); 5.12 and 5.25 (both m, together 1 H); 5.90 and 5.99 (both br, together 1 H); 6.60 (m, 1 H); 7.10 - 7.85 (m, 12 H).

25

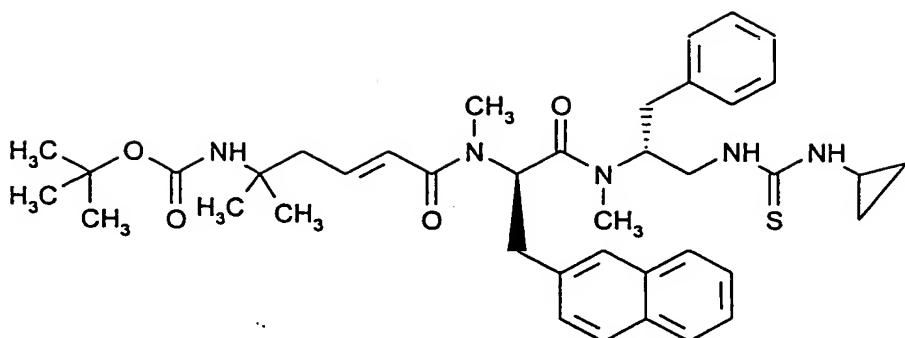
(2R)-N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.



N-((1R)-1-(N-((1R)-1-(3-Cyclopropylthioureido)methyl)-2-phenylethyl)-
 5 N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester (579
 mg, 1.01 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled
 to 0 °C. Trifluoroacetic acid (2 ml) was added. The solution was stirred for 5 min.
 The solvents were removed in vacuo without warming. The residue was dissolved
 in dichloromethane (100 ml) and the solvent was removed in vacuo. This latter
 10 procedure was repeated two times. The crude product was purified by flash
 chromatography on silica (45 g) using dichloromethane/methanol/25% aqueous
 ammonia 100:10:1 as eluent to give 201 mg of (2R)-N-((1R)-1-benzyl-2-(3-
 cyclopropylthioureido)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

15 ¹H-NMR (CDCl₃): δ 0.63 (m, 2H); 0.85 (m, 2 H); 1.90 (s, 3 H); 2.38 (br, 1 H); 2.65 (s,
 3 H); 2.70 - 3.05 (m, 5 H); 3.60 (m, 1 H); 4.05 (m, 1 H); 5.23 (m, 1 H), 6.30 (m, 1 H);
 6,90 - 7.85 (m, 13 H).

(3E)-4-(N-((1R)-1-(N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-
 20 N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-
 enylcarbamic acid tert-butylester



(2E)-5-tert-Butoxycarbonylamino-5-methylhex-2-enoic acid (182 mg, 0.75 mmol)

5 was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). 1-Hydroxy-7-azabenzotriazole (102 mg, 0.75 mmol) was added. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (144 mg, 0.75 mmol) was added. The solution was stirred for 15 min at 0 °C. (2R)-N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-

10 2-methylamino-3-(2-naphthyl)propionamide (178 mg, 0.37 mmol) was dissolved in dichloromethane and added to the reaction mixture. Ethyldiisopropylamine (0.13 ml, 0.75 mmol) was added. The solution was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (200 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (100 ml). The aqueous solution

15 was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (150 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (45 g) to give 89 mg of

(3E)-4-((1R)-1-(N-((1R)-1-benzyl-2-(3-

20 cyclopropylthioureido)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃, selected values): δ -0.08, 0.11, 0.20, 0.30, and 0.60 (all m, together 4 H); 3.34 (dd, 1 H); 4.00 (m, 1 H); 5.52 and 5.87 (dd, 1 H); 6.00 and 6.05 (both d, 25 together 1 H); 6.65 and 6.80 (both m, together 1 H).

(3E)-4-(N-((1R)-1-(N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butylester (63 mg, 0.09 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoracetic acid (2 ml) was added. The solution was stirred for 15 min at 0 °C. The solvent was removed in vacuo at 20 °C. The residue was dissolved in dichloromethane (50 ml), and the solvent was removed in vacuo. This latter procedure was repeated two times. The residue was dissolved in ethyl acetate (2 ml). Heptane (5 ml) was added. The precipitation was filtered off and was characterized to be 50 mg of the title compound as trifluoroacetic acid salt.

¹H-NMR (DMSO-d₆, selected values): δ 0.25 - 0.75 (m, 4 H); 3.15 (dd, 1 H); 6.41 (m, 1 H).

HPLC:

The RP-HPLC analysis was performed using UV detection at 254nm and a Lichrosorp RP-18 5mM column, which was eluted at 1ml/minute. Two solvent systems were used:

Solvent system I: 0.1% Trifluoro acetic acid in acetonitrile. Solvent system II: 0.1% Trifluoroacetic acid in water.

The column was equilibrated with a mixture composed of 20% of solvent system I and 80% of solvent system II. After injection of the sample a gradient of 20% to 80% of solvent system I in solvent system II was run over 30 minutes. The gradient was then extended to 100% of solvent system I over 5 minutes followed by isocratic elution with 100% of this system for 6 minutes.

R_t 20.42 min.

30

MS: found 599.6 [M+H]⁺, calc: 599.3.

m.p.: 138 - 145 °C.

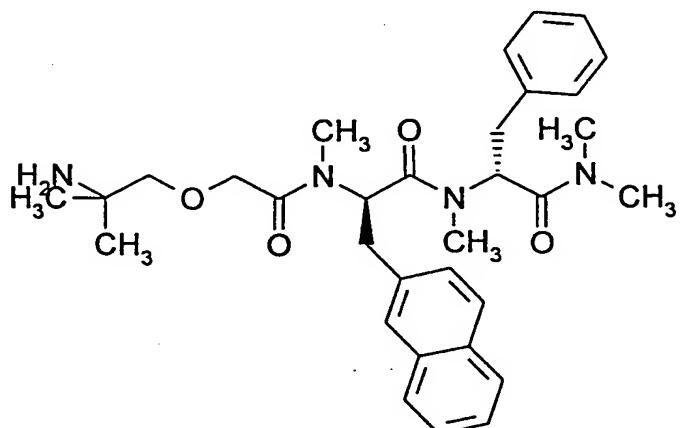


5 calc.: C 59.26 H 6.72 N 9.34
found: C 59.23 H 6.64 N 8.83.

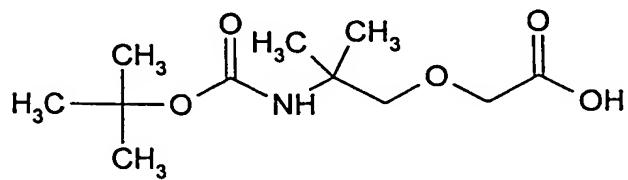
Example 59

10

(2R)-2-(N-[{2-Amino-2-methylpropoxy}acetyl]-N-methylamino)-N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide:



15 (2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid:



A solution of 2-tert-butoxycarbonylamino-2-methylpropanol (5.0 g, 26 mmol) and rhodium(II)acetate (90 mg) in 1,2-dichloroethane (500 ml) was heated to 80 °C. Then ethyl diazoacetate (4.0 g, 35 mmol) was added over a period of 20 1 h, and the mixture was stirred at reflux for 3 h. Another portion of rhodium(II)acetate (90 mg) was added and the mixture was refluxed for

another 5 h. The mixture was cooled overnight and saturated sodium bicarbonate (500 ml) was added, the phases were separated and the organic layer was washed with saturated sodium bicarbonate (2 x 200 ml), dried (magnesium sulfate) and concentrated in vacuo. The obtained product
5 was dissolved in 1 M lithium hydroxide in methanol/water 3:1 (200 ml) and stirred overnight. The solvent was removed in vacuo, water was added (pH>9) and the mixture was washed with ether (200 ml). Then 1 M hydrochloric acid was added until pH<4 and the mixture was extracted with ethyl acetate (200 ml), dried (magnesium sulfate) and concentrated in vacuo
10 to give 2.5 g of (2-tert-butoxycarbonylamino-2-methylpropoxy)acetic acid.

$^1\text{H-NMR}$ (CDCl_3): d 1.3 (s, 6H) 1.45 (s, 9H) 3.5 (s, 2H) 4.15 (s, 2H) 9.9 (b, 1H).

15 To a solution of 2-tert-butoxycarbonylamino-2-methylpropoxy)acetic acid (480 mg, 1.9 mmol) in dichloromethane (10 ml) were added 1-hydroxy-7-azabenzotriazole (264 mg, 1.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (409 mg, 2.1 mmol) and the mixture was stirred for 30 min. Then (2R)-N-((1R)-1-dimethylcarbamoyl-
20 2-phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (434 mg, 0.97 mmol) in dichloromethane (5 ml) and diisopropylethylamine (0.22 ml, 1.3 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (20 ml), saturated aqueous sodium bicarbonate (20 ml), water (2 x 20 ml), brine (20 ml), dried
25 over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with ethyl acetate/pentane 7:3 to give 432 mg of (2-[{N-((1R)-1-[N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl]-2-(2-naphthyl)ethyl)-N-methylcarbamoyl}methoxy]-1,1-dimethylethyl)carbamic acid tert-butylester. The obtained product was
30 dissolved in 50% trifluoroacetic acid in dichloromethane (3 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the

phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried (magnesium sulfate) and concentrated in vacuo. The product was redissolved in water (30 ml) and the mixture was lyophilized to give 300 mg of the title compound.

¹H-NMR (CDCl₃) (selected peaks): d 1.2 (d, 6H) 2.2 (s, 6H) 2.7 (s, 3H) 2.8 (s, 3H) 4.0 (q, 2H) 5.7 (m, 1H) 5.8 (m, 1H) 7.1-7.8 (m, 12H).

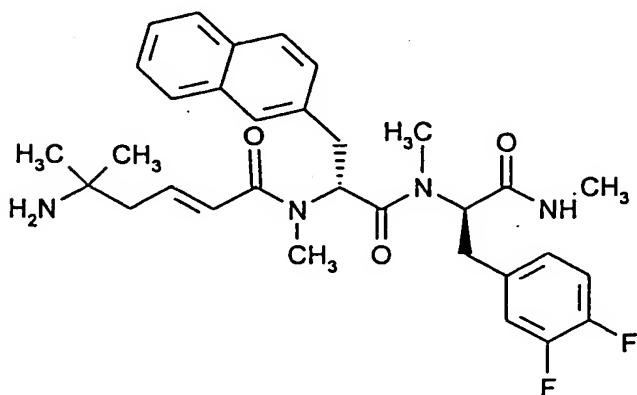
10 HPLC (A1): R_t = 32.8
 (B1): R_t = 34.6

LC-MS: 547.0 (M+H)⁺

15

Example 60

5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
 2-(3,4-difluorophenyl)-1-methylcarbamoylethyl)methylcar-
 20 bamoyl)-2-(2-naphthyl)ethyl)methylamide



This compound was prepared analogously to example 1. 2-(3,4-difluorophenyl)-alanine was substituted for phenylalanine.

5 $^1\text{H-NMR}$ (CDCl_3): (selected peaks for major rotamer) d 1.22 (s, 6H); 2.10 (d, 3H); 2.71 (s, 3H); 2.85 (s, 3H); 5.22 (dd, 1H); 5.86 (dd, 1H); 6.17 (d, 1H).

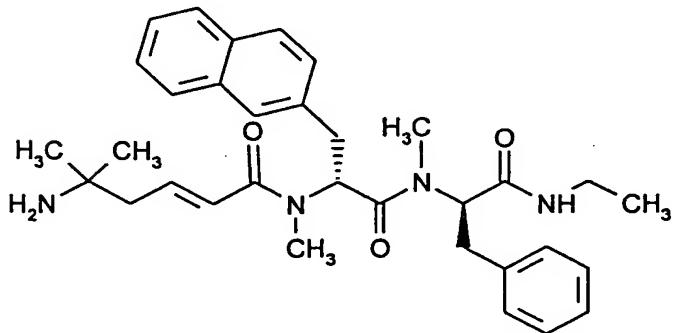
HPLC : $r_t = 33.18$ min. (A1)

PDMS : m/z 566.0 ($\text{M}+\text{H})^+$

10

Example 61

5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
15 2-phenyl-1-ethylcarbamoylethyl)methylcar-
bamoyl)-2-(2-naphthyl)ethyl)methylamide



20 This compound was prepared analogously to example 1.

$^1\text{H-NMR}$ (CDCl_3): (selected peaks for major rotamer) d 0.61 (t, 3H); 1.05 (s, 6H); 1.98 (s, 3H); 2.24 (s, 3H); 2.97 (d, 3H); 5.57 (dd, 1H); 5.85 (dd, 1H); 6.07 (d, 1H).

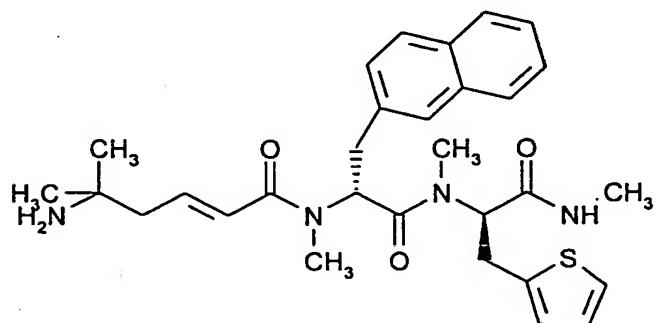
25 HPLC : $r_t = 33.0$ min (A1)

PDMS : m/z 544.0 (M+H)⁺

Example 62

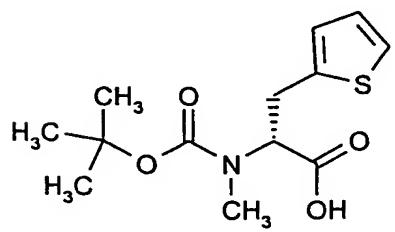
5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl) ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide



10

15 (2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(thiophen-2-yl)propionic acid



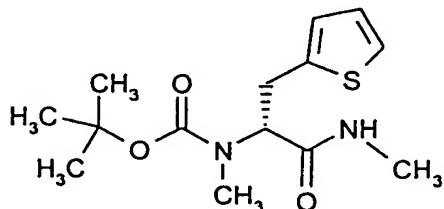
20 (2R)-2-(tert-Butoxycarbonylamino)-3-(thiophen-2-yl)propionic acid (5.00 g; 18.4 mmol) was dissolved in tetrahydrofuran (60 ml). Methyl iodide (9.2 ml; 147 mmol) was added and the solution was cooled to 0°C. Sodiumhydride (60 % in oil; 1.90 g;

55.3 mmol) was added in portions and the reaction mixture was stirred at room temperature for two days. Ethyl acetate (50 ml) and water (20 ml) were added dropwise. The solvent was removed in vacuo and the residue was dissolved in ether (30 ml) and water (30 ml). The phases were separated and the organic phase
 5 was washed with saturated aqueous sodium hydrogencarbonate (30ml). The aqueous phase were mixed. Citric acid (5% (aq)) was added to pH 3 and the aqueous phase was extracted with ethyl acetate (4 x 30 ml). The combined organic phases were washed with water (2 x 30 ml), aqueous sodium thiosulfate (5%; 30 ml), water (30 ml) and dried over magnesium sulfate. The solvent was removed in
 10 vacuo. The residue was dissolved in ether (10 ml) and dicyclohexylamine (8.5 ml) was added and the mixture was left in a refrigerator overnight. The precipitate was filtered and washed with ether (2 x 15 ml) and then redissolved in methylene chloride and washed with a mixture of water (15 ml) and sodium hydrogensulfate (15 ml; 10 %(aq)). The aqueous phase was washed with methylene chloride (3 x 15
 15 ml). The combined organic phases were dried over magnesium sulfate and the solvent was removed in vacuo to give 5.10 g of (2R)-2-(N-(tert-Butoxycarbonyl))-N-methylamino)-3-(thiophen-2-yl)propionic acid.

20

¹H-NMR: (CDCl₃) (major rotamer) d 1.38 (s, 9H); 2.85 (s, 3H); 3.14 (dd, 1H); 3.56 (dd, 1H); 4.62 (dd, 1H); 6.80-7.11 (3 arom. H).

25 N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamic acid
 tert-butylester

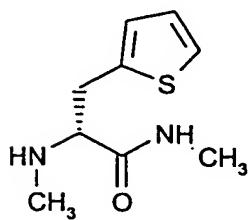


(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(thiophen-2-yl)propionic acid (2.00 g; 7.01 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxybenzotriazole (0.95 g; 7.01 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) 5 carbodiimide hydrochloride (1.48 g ; 7.71 mmol) were added. The solution was stirred for 15 min. at roomtemperature. Methylamine (40 % in methanol; 0.38 ml; 7.71 mmol) and diisopropylamine (1.2 ml; 7.01 mmol) were added and the reaction mixture was stirred at room temperature for two days. Water (10 ml) and methylene chloride (10 ml) were added to the solution. The phases were separated and the 10 organic phase was washed with aqueous sodium hydrogensulfate (10%; 15 ml), saturated aqueous sodium hydrogencarbonate (15 ml), dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was chromatographed on silica (4 x 40 cm) with ethyl acetate/methylene chloride (1:1) as eluent to give 1.18 g of N-Methyl-N-

15 (1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamic acid tert-butylester.

¹H-NMR : (CDCl₃) (major rotamer) d 1.42 (s, 9H); 2.80 (s, 6 H); 3.20 (m, 1H); 3.49 (dd, 1H) ; 4.92 (dd, 1H); 6.81- 7.18 (arom.; 3H).

20 (2R)-N-Methyl-2-methylamino-3-(thiophen-2-yl)propionamide



25 N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamic acid tert-butylester (1.17 g ; 3.92 mmol) was dissolved in methylene chloride (4 ml). The reaction was cooled to 0°C and trifluoroacetic acid was added. The mixture was stirred at room temperature for 1.5 hour. Water (30 ml) and solid sodium

hydrogencarbonate were added to pH 8. The phases were separated. The aqueous phase was extracted with methylene chloride (4 x 20 ml). The combined organic phases were dried over magnesium sulfate and the solvent was removed over vacuo to afford 0.70 g of

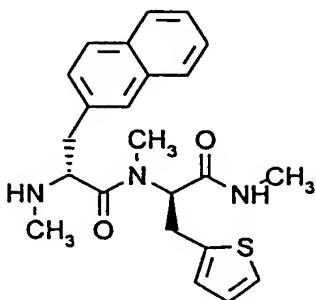
- 5 (2R)-N-methyl-2-methylamino-3-(thiophen-2-yl)propionamide.

¹H-NMR : (CDCl₃) d 2.35 (s; 3H); 2.85 (d; 3H); 3.08 (dd; 1H); 3.25 (dd ; 1H); 3.39 (dd; 1H); 6.88 - 7.29(arom.; 3H)

- 10 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) carbamic acid tert butylester.
- 15 2-(tert Butoxycarbonylmethylamino)-3-(2-naphthyl) propionic acid (1.20 g ; 3.55 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxy-7-azabenzotriazol (0.48 g ; 3.55 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.75 g ; 3.90 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.
- 20 (2R)-N-Methyl-2-methylamino-3-(thiophen-2-yl)propionamide (0.70 g; 3.55 mmol) was dissolved in methylene chloride (10 ml) and added. Diisopropylamine (0.61 ml ; 3.55 mmol) was added. The reaction mixture was stirred at room temperature for 2 days. Methylene chloride (10 ml) and water (10 ml) were added to the reaction mixture. The phases were separated and the
- 25 organic phase was washed with aqueous sodium hydrogensulfate (10%; 20 ml), saturated aqueous sodium hydrogencarbonate (20 ml). The organic phase was dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was chromatographed on silica (2 x 20 cm) using ethylacetate/heptane (1:1) as eluent to afford 1.38 g of
- 30 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) carbamic acid tert butylester.

¹H-NMR : (CDCl₃) (selected peaks for major rotamer) d 1.33 (s, 9H); 2.27 (d, 3H); 2.81 (s, 3H); 2.95 (s, 3H); 5.02 (dd, 1H); 5.22 (dd, 1H).

5 (2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)-3-(2-naphthyl)propionamide



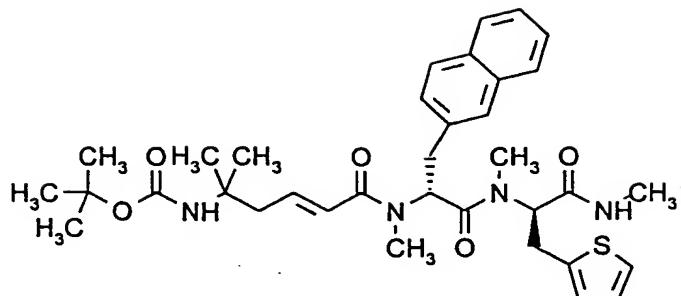
10 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) carbamic acid tert butylester (1.38 g ; 2.71 mmol) was dissolved in methylene chloride (6 ml) and trifluoroacetic acid (4 ml) was added. The reaction mixture was stirred for 1 hour at room temperature. Water (30 ml) and solid sodium hydrogencarbonate were added to pH 8. The 15 phases were separated and the aqueous phase was extracted with methylene chloride (4 x 20 ml). The organic phase was dried over magnesium sulfate and the solvent was removed over vacuo to afford 1.06 g of (2R)-N-methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)-3-(2-naphthyl)propionamide.

20

¹H - NMR : (CDCl₃) (selected peaks for major rotamer) d 1.95 (s, 3H); 2.28 (d, 3H); 2.55 (s, 3H); 3.90 (dd, 1H); 5.42 (dd, 1H).

25 ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carba

mic acid tert butylester.



5

(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.30 g ; 1.22 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxy-7-azabenzotiazole (0.17 g; 1.22 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g ; 1.34 mmol) were added. The reaction mixture was stirred 10 for 15 min at room temperature.

(2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)-3-(2-naphthyl)propionamide (0.50 g; 1.22 mmol) in methylene chloride (10 ml) was added to the reaction mixture. Diisopropylamine (0.21 ml; 1.22 mmol) was added. The reaction mixture was stirred 12 hours at room temperature. Water (10 ml) and methylene chloride (10 ml) were added. The phases were separated and the organic phase was washed with aqueous sodium hydrogensulfate (10%; 20 ml), saturated aqueous sodium hydrogencarbonate (20 ml), dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was chromatographed on silica (2 x 20 cm) using ethyl acetate/methylene 15 chloride (1:1) as eluent to afford 0.66 g of

((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carba 20 mic acid tert butylester.

25

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-

2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester (0.66g; 1.04 mmol) was dissolved in methylene chloride (3 ml) and trifluoroacetic acid (2 ml) was added. The reaction mixture was stirred 5 min at room temperature. Water (2 ml) and solid sodium hydrogencarbonate was added to pH 8. The phases were separated and the aqueous phase was extracted with methylene chloride (4 x 15 ml). The organic phase was dried over magnesium sulfate and the solvent was removed in vacuo to afford 0.53 g of the title compound.

10 $^1\text{H-NMR}$ (CDCl_3) (selected peaks for major rotamer) d 2.31 (d, 3H); 2.63 (s, 3H); 2.91 (s, 3H); 5.18 (dd, 1H); 5.55 (dd, 1H); 6.19 (d, 1H).

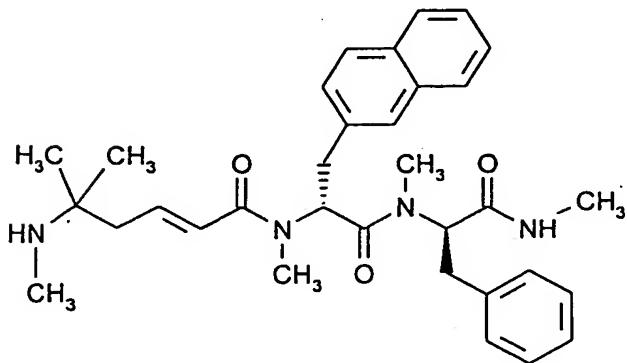
HPLC : $r_t = 30.3$ min (A1).

15 PDMS : m/z 534.8 ($\text{M}+\text{H})^+$

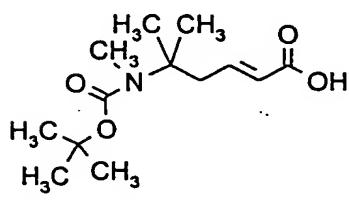
Example 63

(2E)-5-Methyl-5-methylaminohex-2-enoic acid

20 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenyl ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide



(2E)-5-(N-(tert Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid.



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (5.00 g ; 20.6 mmol) was dissolved in tetrahydrofuran (70 ml). Methyl iodide (10.3 ml; 164 mmol) was added and the solution was cooled to 0° C. Sodium hydride (60% in oil)(
 10 2.07 g; 61.6 mmol) was added in portions and the solution was stirred at roomtemperature for four days. Ethyl acetate (70 ml) and water (60 ml) was added dropwise and the solvent was removed in vacuo. The crude product was dissolved in water (40 ml) and ether (40 ml). The organic phase was washed with a saturated aqueous solution of sodium hydrogencarbonate (30 ml). The aqueous
 15 phases were mixed and 5% aqueous citric acid was added to pH 3. The aqueous phase was extracted with ethylacetate (4 x 50-ml). The organic phase was washed with water (2 x 40 ml), an aqueous solution of sodium thiosulfate (5%; 40 ml), water (40 ml), dried over MgSO₄ and the solvent was removed in vacuo. The residue was dissolved in ethylacetate (45 ml) and washed with an aqueous
 20 solution of sodium hydrogensulfate (10%; 3 x 30 ml), dried over MgSO₄ and concentrated in vacuo to give 4.00 g of (2E)-5-(N-(tert
 Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid.

¹H-NMR (CDCl₃) d 1.38 (s, 6H), 1.45 (s, 9H); 2.80 (d, 2H); 2.85 (s, 3H); 5.88 (d,
 25 1H); 7.01 (q, 1H).

The title compound was prepared analogously to example 1. 5-Methylamino-5-methylhex-2-enoic acid was incorporated instead of 5-amino-5-methylhex-2-enoic

acid.

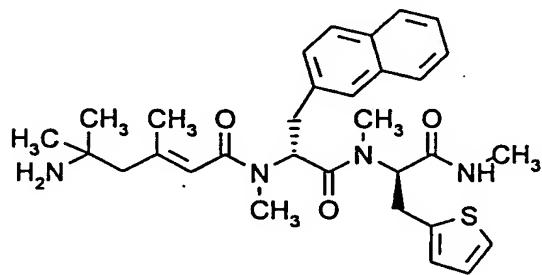
¹H-NMR : (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 3H; 1.30 (s, 3H); 5 2.28 (d, 3H); 2.52 (s, 3H); 2.72 (s, 3H); 2.99 (d, 3H); 5.69 (dd, 1H); 5.81 (dd, 1H); 6.13 (d, 1H).

PDMS: m/z 544.4 (M+H)⁺

10 HPLC : r_t = 31.3 min (A1).

Example 64

15 (2E)-5-Amino-3,5-dimethylhex-2-enoic acid
 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) amide.



20

The title compound was prepared analogously to example 1. 2-thienylalanine was substituted for phenylalanine and 5-amino-3,5-dimethylhex-2-enoic acid was 25 substituted for 5-amino-5-methylhex-2-enoic acid.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.24 (s, 3H); 1.25 (s, 3H); 1.76 (s, 2H); 2.32 (s, 3H); 2.76 (d, 3H); 2.99 (s, 3H); 5.65 (dd, 1H); 5.76 (s, 1H); 5.90 (dd, 1H)

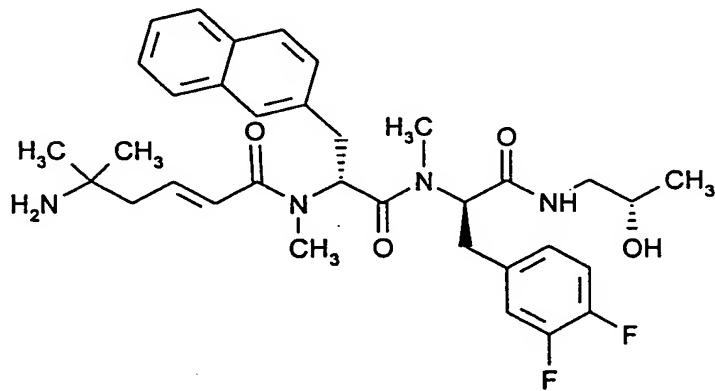
5 HPLC : R_t= 31.45 min.

PDMS : m/z 549.7 (M+H)⁺

10 Example 65

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(3,4-difluorophenyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.

15



This compound was prepared analogously to example 1. 2-(3,4-difluorophenyl)-
20 alanine was substituted for phenylalanine.

¹H-NMR (CDCl₃): (selected peaks for major rotamer) d 1.01 (t, 3H); 1.10 (s, 6H); 2.74 (s, 3H); 3.04 (s, 3H); 5.08 (dd, 1H); 5.56 (dd, 1H); 6.07 (d, 1H).

HPLC : $r_t = 32.9$ min. (A1)

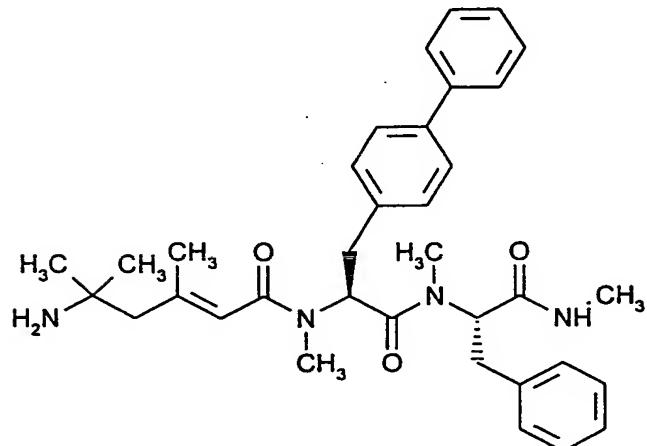
PDMS : m/z 610.3 ($M+H$)⁺

Example 66

5

5-Amino-3,5-dimethylhex-2-enoic acid

N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide.



10

The title compound was prepared analogously to example 1. N-Tert-Butoxycarbonyl-N-methyl-D-biphenylalanin was substituted for N-tert-butoxycarbonyl-N-methyl-D-phenylalanin in step E.
 (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid was substituted for (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid in step I.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 3H); 1.28 (s, 3H); 1.57 (s, 3H); 2.32 (s, 3H); 2.73 (d, 3H); 2.94 (s, 3H); 5.34 (dd, 1H); 5.45 (dd, 1H); 5.75 (s, 1H).

HPLC: $r_t = 35.37$ min (Method A1)

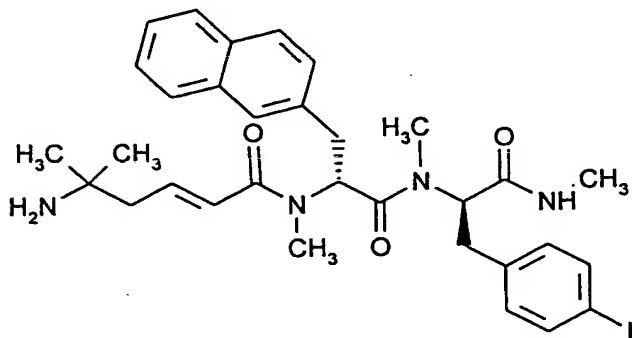
PDMS: m/z = 569.7 (M+H)⁺

5 Example 67

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

10



15 This compound was prepared analogously to example 1. N-tert-Butoxycarbonyl-N-methyl-D-4-iodophenylalanine was substituted for N-tert-butoxycarbonyl-N-methyl-D-phenylalanin in step E.

20 ¹H-NMR (CDCl₃)(selected peaks for major rotamer) d 1.15 (s, 6H); 2.09 (d, 3H); 2.69 (s, 3H); 2.70 (s, 3H); 5.24 (dd, 1H); 5.90 (dd, 1H); 6.18 (d, 1H).

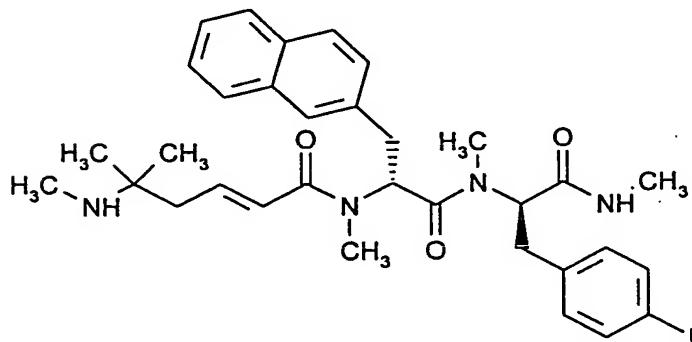
HPLC: r_t = 35,25 min (Method A1)

25 PDMS: m/z = 655.7 (M+H)⁺

Example 68

5 (2E)-5-Methyl-5-methylaminohex-2-enoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



10

This compound was prepared analogously to example 1. N-Tert-butoxycarbonyl-N-methyl-D-4-iodophenylalanin was substituted for N-tert-butoxycarbonyl-N-15 methyl-D-phenylalanin in step E. (2E)-5-(N-(tert-Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid was substituted for (2E)-5-(tert-butyloxycarbonylamino)-5-methylhex-2-enoic acid in step I.

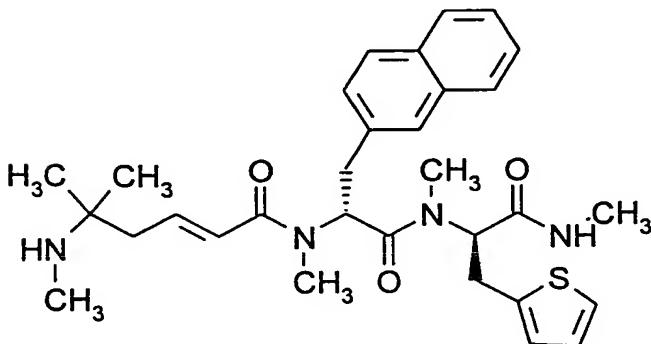
20 ¹H-NMR: (CDCl₃)(selected peaks for major rotamer) d 1.17 (s, 6H); 2.07 (d, 3H); 2.39 (s, 3H); 2.71 (s, 6H); 2.92 (s, 3H); 5.25 (dd, 1H); 5.90 (dd, 1H); 6.20 (d, 1H).

HPLC: r_t = 35.38 min (Method A1)

25 PDMS: m/z = 668.9 (M+H)⁺

Example 69

(2E) 5-Methyl-5-amino-5-methylhex-2-enoic
 acid-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thien-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



10

This compound was prepared analogously to example 1. 2-thienyl-alanine was substituted for phenylalanine and 5-methyl-5-methylaminohex-2-enoic acid was substituted for 5-amino-3,5-dimethylhex-2-enoic acid.

15 $^1\text{H-NMR}$ (CDCl_3): (selected peaks for major rotamer) d 1.25 (s, 3H); 1.28 (s, 3H); 2.26 (d, 3H); 2.68 (s, 3H); 2.95 (s, 3H); 3.06 (s, 3H); 5.25 (dd, 1H); 5.89 (dd, 1H); 6.22 (d, 1H).

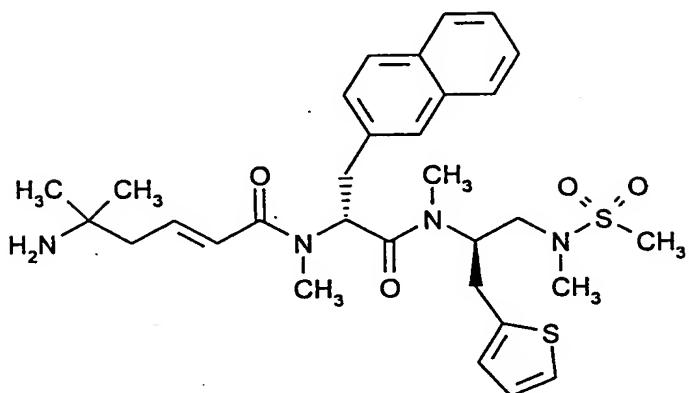
HPLC : $r_t = 30.4$ min.

20 PDMS : m/z 549.2 ($\text{M}+\text{H})^+$

Example 70

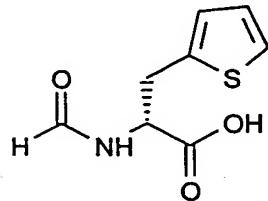
(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-
 25 (methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-

naphthyl)ethyl)hex-2-enamide



5

(2R)-2-(Formylamino)-3-(2-thienyl)propionic acid



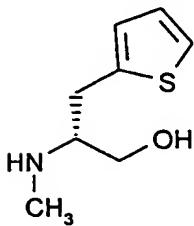
10 (2R)-2-Amino-3-(2-thienyl)propionic acid (5.00 g, 29.2 mmol) was dissolved in formic acid (50 ml). The solution was cooled to 0 °C. Acetic acid anhydride (20 ml) was added dropwise. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was cooled to 0 °C. Water (20 ml) was added dropwise. The solution was warmed to room temperature. The solvent was removed in vacuo. The residue was suspended in ethyl acetate (20 ml). The precipitation was filtered off, collected, and dried in vacuo, to give 3.60 g of crude (2R)-2-(formylamino)-3-(2-thienyl)propionic acid, which was used for the following step.

20 ¹H-NMR (DMSO d₆): δ 3.05 and 3.15 (both ABX, together 1 H); 3.30 and 3.55 (m and ABX, together 1 H); 4.30 and 4.55 (both m, together 1 H); 6.90 (m, 1 H); 6.95

(m, 1 H); 7.35 (d, 1 H); 8.03 (s, 1 H); 8.40 (d, 1 H); 12.92 (br, 1 H).

(2R)-2-Methylamino-3-(2-thienyl)propan-1-ol

5

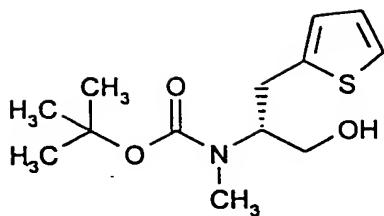


A solution of (2R)-2-(formylamino)-3-(2-thienyl)propionic acid (3.58 g, 18.0 mmol) in tetrahydrofuran (50 ml) was added dropwise to a suspension of sodium borohydride in tetrahydrofuran (50 ml), which was cooled to 7 - 12 °C (inside temperature). After the addition was finished, a solution of iodine (4.57 g, 18.0 mmol) in tetrahydrofuran (100 ml) was added dropwise. The reaction mixture was heated to reflux for 16 h. It was cooled to 0 °C. Methanol (200 ml) was added dropwise. The solvent was removed in vacuo. The residue was dissolved in a freshly prepared 20% aqueous sodium hydroxide solution (200 ml). The aqueous phase was extracted with tert-butyl methyl ether (4 x 150 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo to give 3.26 g of crude (2R)-2-methylamino-3-(2-thienyl)propan-1-ol, which was used for the following step.

20

¹H-NMR (DMSO d₆, selected values): d 2.32 (s, 3 H); 2.56 (m, 1 H); 2.84 (m, 2 H); 3.30 (m, 2 H); 6.85 (m, 1 H); 6.93 (m, 1 H); 7.28 (d, 1 H).

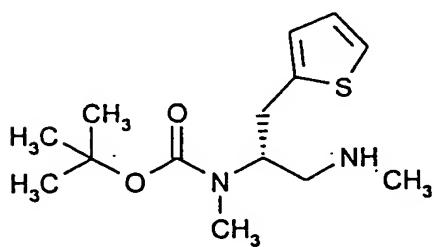
25 N-((1R)-1-(Hydroxymethyl)-2-(2-thienyl)ethyl)-N-methylcarbamic acid tert-butyl ester



A solution of di-tert-butyldicarbonate (4.97 g, 22.8 mmol) in tetrahydrofuran (20 ml) was added dropwise to a solution of (2R)-2-methylamino-3-(2-thienyl)propan-1-ol in 1 N aqueous sodium hydroxide solution (19 ml) and tetrahydrofuran (20 ml). The reaction mixture was stirred at room temperature for 16 h. It was diluted with water (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (220 g), using ethyl acetate/heptane 1:1 as eluent, to give 3.85 g of N-((1R)-1-(hydroxymethyl)-2-(2-thienyl)ethyl)-N-methylcarbamic acid tert-butyl ester.

15 ¹H-NMR (CDCl₃, selected values) δ 1.41 (br, 9 H); 2.75 (br, 3 H); 3.05 - 3.20 (both br, together 2 H); 3.75 (br, 2 H); 4.10 and 4.27 (both br, together 1 H); 6.82 (br, 1 H); 6.90 (m, 1 H); 7.14 (d, 1 H).

20 N-Methyl-N-((1R)-2-methylamino-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester

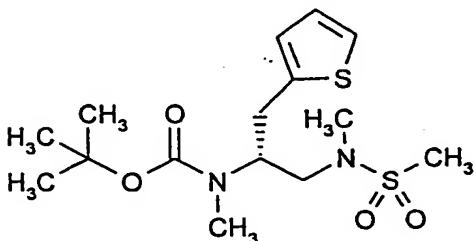


A solution of oxalyl chloride (1.81 ml, 20.8 mmol) in dichloromethane (180 ml) was cooled to -78 °C. A solution of dimethylsulfoxide (2.15 ml, 27.8 mmol) in dichloromethane (2 ml) was added dropwise. The solution was stirred for 15 min at -78 °C. A solution of N-((1R)-1-(hydroxymethyl)-2-(2-thienyl)ethyl)-N-
 5 methylcarbamic acid tert-butyl ester (3.78 g, 13.9 mmol) in dichloromethane (10 ml) was added dropwise. The solution was stirred for 20 min at -78 °C.
 Triethylamine (7.71 ml, 55.6 mmol) was added. The solution was stirred for 5 min at -78 °C and warmed to -35 °C. As soon as -35 °C was reached it was cooled to -78 °C. Acetic acid (3.50 ml, 61.2 mmol) was added. The solution was warmed to
 10 room temperature and was washed with brine (200 ml). The organic phase was dried over magnesium sulfate. The solvent was removed in vacuo. The residue was dissolved in methanol (180 ml). 4 Å mol (20 g) sieves was added. Acetic acid (5.5 ml, 97.3 mmol) was added. An 8.0 M solution of methylamine in ethanol (5.2 ml, 41.7 mmol) was added. Solid sodium cyano borohydride (0.57 g, 9.1 mmol)
 15 was added. The solution was stirred at room temperature for 1 h, before another portion of solid sodium cyano borohydride (0.57 g, 9.1 mmol) was added. The reaction mixture was stirred for 16 h at room temperature and filtered through a plug of celite. The celite was washed with methanol (150 ml). The solvent of the filtrate was removed in vacuo. The residue was dissolved in 1 N sodium
 20 hydroxide solution (200 ml). The solution was extracted with tert-butyl methyl ether (3 x 100 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (150 g), using dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent, to give 1.72 g of N-methyl-N-((1R)-2-
 25 methylamino-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values) d 1.32 and 1.42 (both br, together 9 H); 2.44 (s, 3 H); 2.63 (ABX, 1 H); 2.70 - 2.90 (m, 4 H); 2.95 and 3.03 (both br, together 2 H); 4.40 (br, 1 H); 6.82 (br, 1 H); 6.92 (m, 1 H); 7.15 (d, 1 H).

N-Methyl-N-((1R)-2-(N-methyl-N-(methylsulfonyl)amino)-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester

5

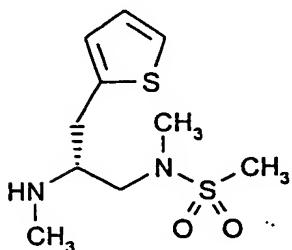


N-Methyl-N-((1R)-2-methylamino-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester (1.72 g, 6.05 mmol) was dissolved in dichloromethane (30 ml).

10 Triethylamine (0.84 ml, 6.05 mmol) was added. The solution was cooled to -78 °C. Methanesulfonyl chloride (0.47 ml, 6.05 mmol) was added dropwise. The reaction mixture was warmed to room temperature over a period of 3.5 h. It was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (100 ml). It was washed with 10% aqueous sodium hydrogen sulfate solution (200 ml). The aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (180 g), using ethyl acetate/heptane 1:1 as eluent, to give 1.94 g of N-methyl-N-((1R)-2-(N-methyl-N-(methylsulfonyl)amino)-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester.

25 ¹H-NMR (CDCl₃) δ 1.40 and 1.45 (both s, together 9 H); 2.74 and 2.80 (s and m, together 6 H); 2.91 (s, 3 H); 3.06 (m, 3 H); 3.57 (m, 1 H); 4.55 (br, 1 H); 6.85 (d, 1 H); 6.92 (m, 1 H); 7.16 (m, 1 H).

N-Methyl-N-((2R)-2-(methylamino)-3-(2-thienyl)propyl)methanesulfonamide

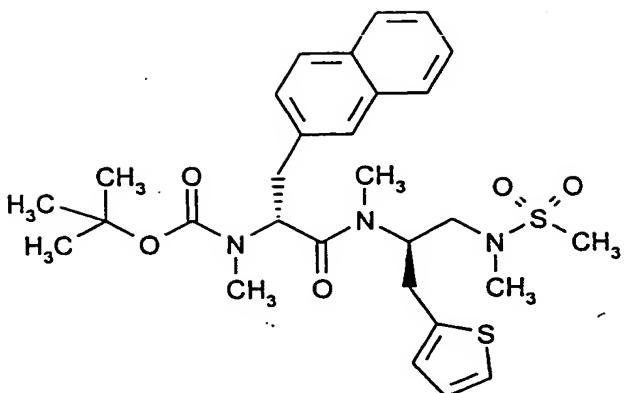


5 A solution of N-methyl-N-((1R)-2-(N-methyl-N-(methylsulfonyl)amino)-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester (1.87 g, 7.12 mmol) in dichloromethane (7 ml) was cooled to 0 °C. Trifluoroacetic acid (7 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. Dichloromethane (10 ml) was added. A saturated aqueous solution of sodium hydrogen carbonate (10 ml) was 10 added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic phases were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (120 g), 15 using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 1.24 g of N-methyl-N-((2R)-2-(methylamino)-3-(2-thienyl)propyl)methanesulfonamide.

¹H-NMR (CDCl₃) δ 2.47 (s, 3 H); 2.81 (s, 3 H); 2.88 (s, 3 H); 2.90 - 3.10 (m, 4 H); 3.22 (dd, 1 H); 6.86 (m, 1 H); 6.95 (m, 1 H); 7.19 (m, 1 H).

20

N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester

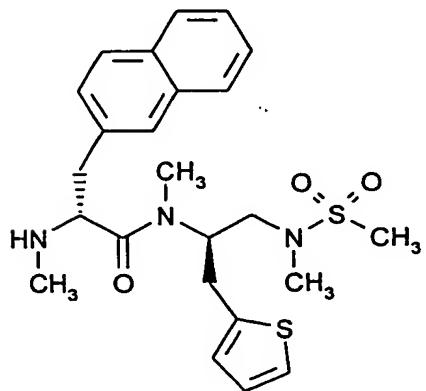


(2*R*)-2-(*N*-(tert-Butoxycarbonyl)-*N*-methylamino)-3-(2-naphthyl)propionic acid

- 5 (1.46 g, 4.42 mmol) was dissolved in *N,N*-dimethylformamide (5 ml) and dichloromethane (5 ml). 1-Hydroxy-7-azabenzotriazole (0.60 g, 4.42 mmol) was added. The solution was cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.85 g, 4.42 mmol) was added. The reaction mixture was stirred for 20 min at 0 °C. A solution of *N*-methyl-*N*-((2*R*)-2-(methylamino)-3-(2-thienyl)propyl)methanesulfonamide (1.16 g, 4.42 mmol) in dichloromethane (5 ml) and ethyldiisopropylamine (0.76 ml, 4.42 mmol) were added successively. The solution was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (90 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (240 g), using ethyl acetate/heptane 2:1 as eluent, to give 2.05 g of *N*-Methyl-*N*-((1*R*)-1-(*N*-methyl-*N*-((1*R*)-1-(*N*-methyl-*N*-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values) δ 1.09 and 1.33 (both s, together 9 H); 5.05 and 5.37 (both dd, together 1 H).

(2R)-2-Methylamino-N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide

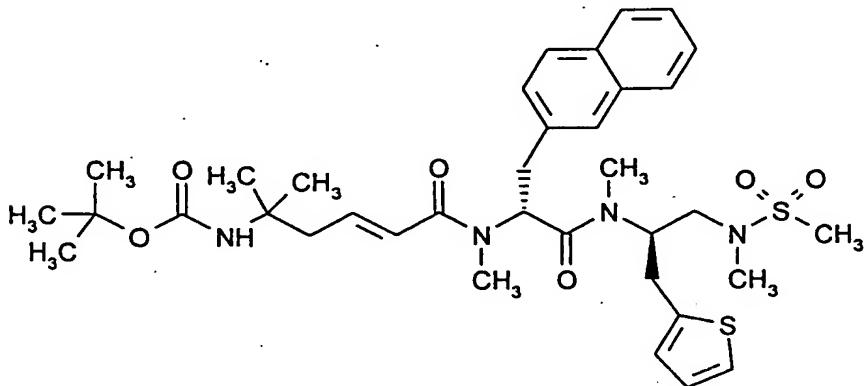


5

A solution of N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester (1.94 g, 3.37 mmol) in
 10 dichloromethane (7 ml) was cooled to 0 °C. Trifluoroacetic acid (7 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (30 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous solution was extracted
 15 with dichloromethane (2 x 50 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (200 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 1.70 g of (2R)-2-Methylamino-N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide.

¹H-NMR (CDCl₃, selected values) δ 2.04 and 2.32 (both s, together 3 H); 2.61 and 2.65 (both s, together 3 H); 2.71 and 2.73 (both s, together 3 H); 2.82 and 2.85 (both s, together 3 H); 3.68 and 3.75 (both t, together 1 H); 5.14 (br, 1 H).

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester



(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (158 mg, 0.65 mmol) was dissolved in N,N-dimethylformamide (3 ml) and dichloromethane (3 ml). 1-10 Hydroxy-7-azabenzotriazole was added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (88 mg, 0.65 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C. A solution of (2R)-2-Methylamino-N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide in dichloromethane (3 ml) and 15 ethyldiisopropylamine (0.12 ml, 0.65 mmol) were added successively. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (50 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (50 ml). The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The organic layers were washed with a 20 saturated aqueous solution of sodium hydrogen carbonate (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified on silica (120 g), using ethyl acetate/heptane 2:1 (250 ml) and successively ethyl acetate/heptane 3:1 as eluent, to give 282 mg of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-

naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values) d 1.15 - 1.35 (m, 6 H); 1.40 and 1.69 (m and br, together 9 H); 5.69 and 5.85 (both m, together 1 H); 6.06, 6.13, and 6.27 (all d, s together 1 H).

A solution of ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester (251 mg, 0.36 mmol) in dichloromethane (3 ml) was cooled to 0 °C. Trifluoroacetic acid (3 ml) was added. The solution was stirred for 50 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (15 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (70 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried two times over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (120 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 159 mg of the title compound. The HPLC showed a 20% impurity, which is a diastereoisomeric of the title compound.

¹H-NMR (CDCl₃, selected values) d 1.14 (br, 6 H); 5.05 (br, 1 H); 5.66, 5.77, and 5.85 (all dd, together 1 H); 6.08, 6.13 and 6.40 (all dd, together 1 H).

MS 598.8 [M+1]⁺;
599.0 [M+1]⁺, isomeric impurity.

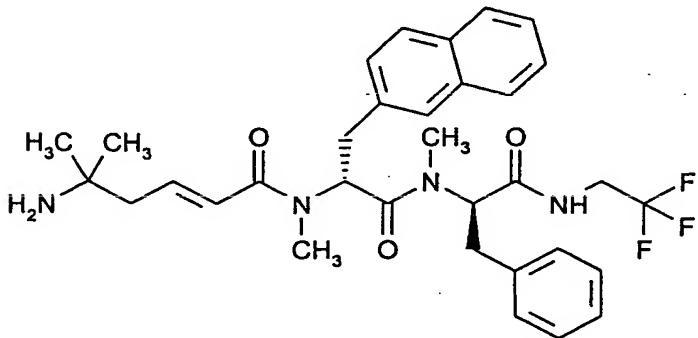
HPLC 31.22 min (A1);
32.75 min (A1, isomeric impurity);
33.18 min (B1);
34.88 min (B1, isomeric impurity).

For biological testing, the title compound was transferred into its acetate salt, by liophilization from 0.5 M acetic acid (50 ml).

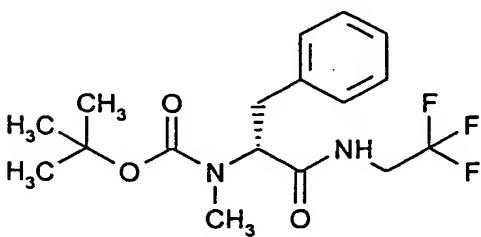
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Example 71

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide



N-Methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamic acid
15 tert-butyl ester



At 0 °C, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.18 g, 20 11.4 mmol) was added to a solution of (2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionic acid (3.0 g, 11.4 mmol) and 1-hydroxybenzotriazole hydrate (1.54 g, 11.4 mmol) in N,N-dimethylformamide (2

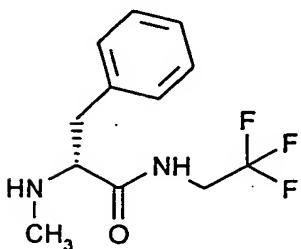
ml) and dichloromethane (4 ml). The reaction mixture was stirred for 15 min at 0 °C. 2,2,2-Trifluoroethylamine (0.91 ml, 11.4 mmol) and ethyldiisopropylamine (2.0 ml, 11.39 mmol) were added successively. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (150 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (200 ml). The aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (150 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silcia (240 g), using ethyl acetate/heptane 1:2 as eluent, to give 3.52 g of N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl_3): d 1.30 and 1.42 (both br, together 9 H); 2.76 (s, 3 H); 3.04 (m, 1 H); 3.35 and 3.48 (both m, together 1 H); 3.65 and 3.85 (both m, together 1 H); 4.13 (m, 1 H); 4.74 and 4.92 (both br, together 1 H); 5.25 and 6.75 (both br, together 1 H); 7.10 - 7.40 (m, 5 H).

MS: 361.0 [M+1]⁺; 261.0 [M+1-BOC]⁺.

20

(2R)-2-Methylamino-3-phenyl-N-(2,2,2-trifluoroethyl)propionamide



25 N-Methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamic acid tert-butyl ester (3.45 g, 9.57 mmol) was dissolved in dichloromethane (8 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (8 ml) was added. The reaction

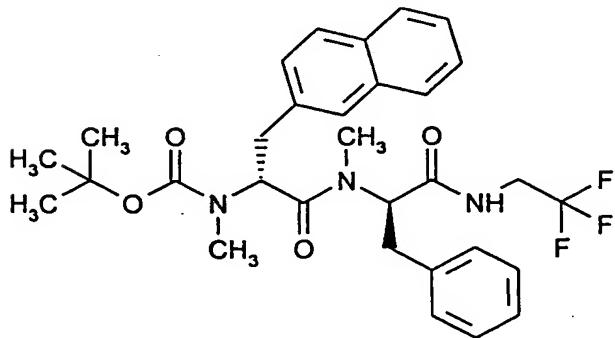
mixture was stirred for 45 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (40 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (180 g), using dichloromethane/methanol/25% aqueous ammonia as eluent to give 1.13 g of (2R)-2-methylamino-3-phenyl-N-(2,2,2-trifluoroethyl)propionamide.

10

¹H-NMR (CDCl₃): δ 2.27 (s, 3 H); 2.73 (dd, 1 H); 3.15 - 3.35 (m, 2 H); 3.95 (m, 2 H); 7.15 - 7.40 (m, 5 H); 7.70 (br, 1 H).

15

N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester



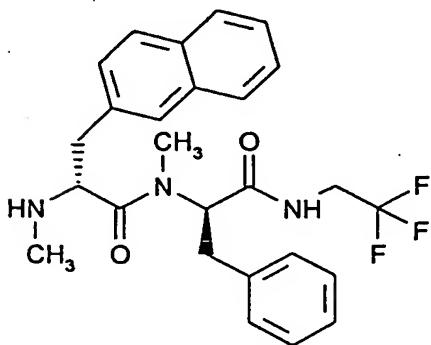
20

A solution of (2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (1.35 g, 4.1 mmol) and 1-hydroxy-7-azabenzotriazole (0.56 g, 4.1 mmol) in N,N-dimethylformamide (5 ml) and dichloromethane (5 ml) was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.79 g, 4.1 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C. A solution of (2R)-2-methylamino-3-phenyl-N-(2,2,2-

trifluoroethyl)propionamide (1.07 g, 4.1 mmol) in dichloromethane (5 ml) was added. Ethyldiisopropylamine (0.71 ml) was added. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (100 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (170 g), using ethyl acetate/heptane 1:2 (300 ml), and then ethyl acetate/heptane/dichloromethane 1:1:1 as eluent to give 1.14 g of N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester.

15 ¹H-NMR (CDCl₃, selected values): δ 1.09 and 1.31 (both s, together 9 H); 5.00 - 5.50 (m, together 2 H); 7.00 - 7.80 (m, 12 H).

20 (2R)-2-Methylamino-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)propionamide



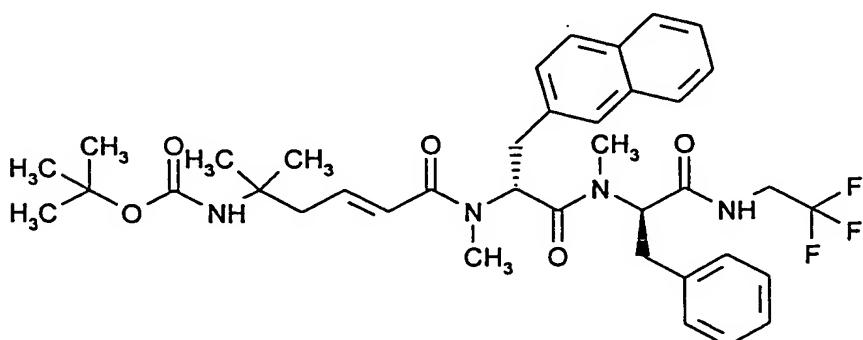
25 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-

butyl ester (1.12 g, 1.97 mmol) was dissolved in dichloromethane (6 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (6 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. A saturated solution of aqueous sodium hydrogen carbonate (30 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added until a clear solution was obtained. The phases were separated. The aqueous solution was extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (90 g), using

10 dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent, to give 946 mg of (2R)-2-methylamino-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)propionamide.

15 ¹H-NMR (CDCl₃, selected values): δ 1.77, 2.36, 2.65, and 2.91 (all s, together 6 H); 4.56 and 5.55 (both dd, together 1 H); 6.85 - 7.90 (m, together 12 H).

20 ((3E)-4-(N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester



25 (2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (168 mg, 0.69 mmol) and 1-hydroxy-7-azabenzotriazole (94 mg, 0.69 mmol) were dissolved in N,N-dimethylformamide (3 ml) and dichloromethane (3 ml). The solution was cooled to

0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (132 mg, 0.69 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C. A solution of (2R)-2-methylamino-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)propionamide (327 mg, 0.69 mmol) in dichloromethane (3 ml) was added. Ethyldiisopropylamine (0.12 ml, 0.69 mmol) was added. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (50 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (50 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (160 g), using ethyl acetate/heptane 1:1 as eluent to give 447 mg of ((3E)-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values): δ 1.20, 1.23, 1.28, and 1.29 (all s, together 15 H); 2.55, 2.76, 2.95, and 3.02 (all s, together 6 H); 7.00 - 7.85 (m, 12 H).

20

((3E)-4-(N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester (407 mg, 0.58 mmol) was dissolved in dichloromethane (4 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (4 ml) was added. The reaciton mixture was stirred for 45 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (5 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified on silica (90 g) using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 251 mg of

the title compound.

¹H-NMR (CDCl₃, selected values): d 1.00 and 1.13 (both s, together 6 H); 2.57, 2.77, 2.98, and 3.06 (all s, together 6 H); 5.30 (m, 1 H); 5.60 and 5.87 (both dd, together 1 H); 6.04 and 6.05 (both d, together 1 H) 6.86 (m, 1 H).

MS: 597.0 [M+1]⁺

HPLC: 35.55 min (A1)

10 37.87 min (B1).

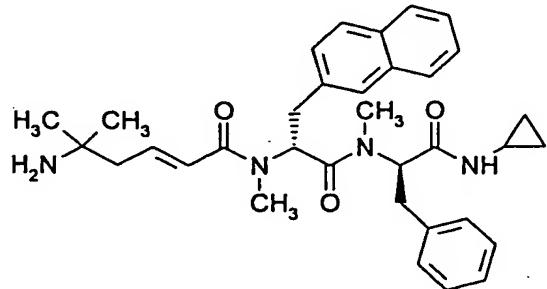
For biological testing, the title compound was transferred into its acetate salt by lyophilization from 0.5 M acetic acid (50 ml).

15 Example 72

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

20



This compound was prepared analogously to example 1 using cyclopropylamine instead of methylamine.

25 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 0.43 (m, 4H); 1.08 (s, 6H); 2.99 (s, 3H); 5.15 (dd, 1H); 5.57 (dd, 1H); 6.04 (d, 1H).

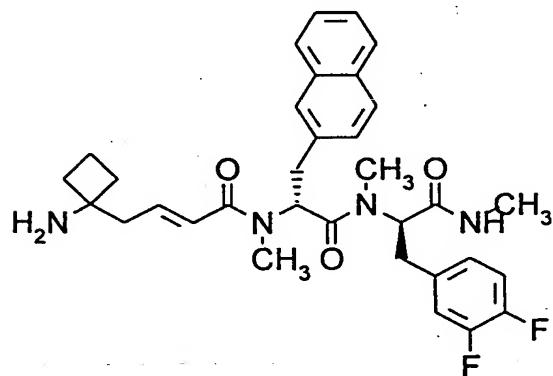
HPLC: $r_t = 33.2$ min (A1)

PDMS: m/z 554 ($M+H$)⁺

5

Example 73

10 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-2-(3,4-difluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



This compound was prepared analogously to example 1 using (3,4-difluorophenyl)alanine instead of phenylalanine and (2E)-4-(tert-butoxycarbonylamino)cyclobutyl)but-2-enoic acid (prepared as in R. Graf, Org Synth. 46, 51 (1966)) instead of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid.

20 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.93 (s, 6H); 2.05 (s, 3H); 2.75 (s, 3H); 2.91 (s, 3H); 5.24 (dd, 1H); 5.92 (dd, 1H); 6.29 (d, 1H)

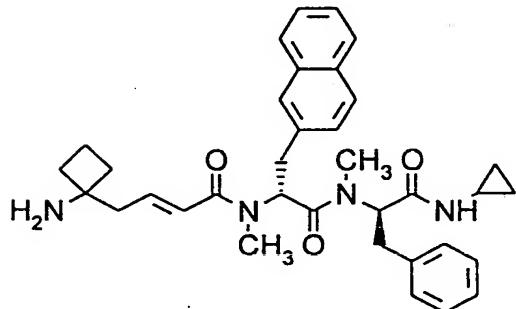
HPLC: $r_t = 33.9$ min (A1)

PDMS: m/z 576 (M+H)⁺

Example 74

5

(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



10

This compound was prepared analogously to example 1 using cyclopropylamine instead of methylamine and (2E)-4-(tert-butoxycarbonylamino)cyclobutyl)but-2-enoic acid (prepared as in R. Graf, Org Synth. 46, 51 (1966)) instead of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid.

15

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 0.45 (m, 4H); 2.49 (s, 20 3H); 2.95 (s, 3H); 5.18 (dd, 1H); 5.78 (dd, 3H); 6.33 (d, 1H)

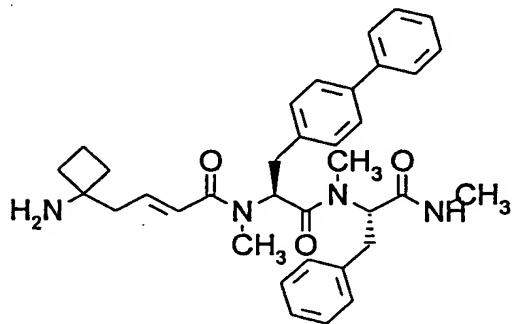
HPLC: r_t = 33.9 min (A1)

PDMS: m/z 567 (M+H)⁺

25

Example 75

(2E) 4-(1-Aminocyclobutyl)-but-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-
 5 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide



This compound was prepared analogously to example 1 using biphenylalanine
 10 instead of phenylalanine and and (2E)-4-(1-(tert-
 buoxycarbonylamino)cyclobutyl)but-2-enoic acid (prepared as in R. Graf, Org
 Synth. 46, 51 (1966)) instead of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-
 2-enoic acid.

15

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.98 (m, 6H); 2.49 (s,
 3H); 2.59 (d, 3H); 2.95 (s, 3H); 5.50 (dd, 1H); 5.78 (dd, 1H); 6.18 (d, 1H).

HPLC: *r*_t = 34.9 min (A1)

20

PDMS: m/z (M+H)⁺

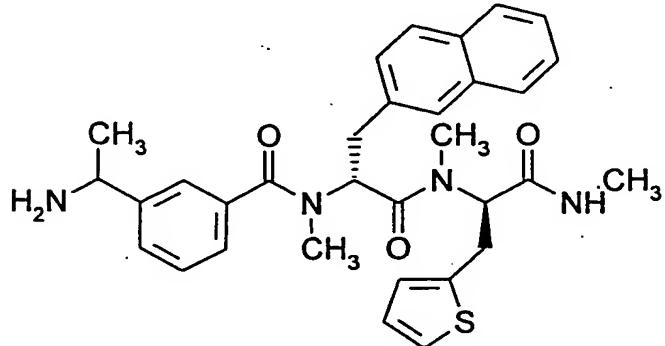
LC-MS: 569.0 (m+1)⁺

25

Example 76

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide

5



The N-Methyl-PAL-Resin (75 mg, 0.045 mmol, load: 0.60) was washed with

- 10 5 % diisopropylethylamine in dichloromethane (2 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (3 x 2 mL) and then swelled in dimethylformamide (2 mL). Then 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid (46 mg, 0.09 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (34 mg, 0.09 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (15 mg, 0.09 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (31 mL, 0.18 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with
- 20 dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (41 mg, 0.09 mmol) in

dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (34 mg, 0.09 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (15 mg, 0.09 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (31 mL, 0.18 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 3-(1-(tert-butoxycarbonylamino)ethyl)-benzoic acid(22 mg, 0.09 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (34 mg, 0.09 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (15 mg, 0.09 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (31 mL, 0.18 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). The resin was cooled to 0 °C and 50 % trifluoroacetic acid in dichloromethane (4 mL) was added and the mixture was shaken for 10 min at 0 °C. The resin was filtered and washed with 50 % trifluoroacetic acid in dichloromethane (2 x 0.5 mL) and the combined filtrates were concentrated under a stream of nitrogen. The obtained product was dissolved in acetonitrile/water 1:20 (10 mL) and applied to a C-18 Sep-Pak Classic© cartridge (0.25 g, purchased from Waters™), which had been prewashed with acetonitrile (10 mL) and water (10 mL). Then water/trifluoroacetic acid 99.9:0.1 (5 mL), followed by water/acetonitrile/trifluoroacetic acid 89.9:20:0.1 (4 mL) was run through the Sep-Pak© and the filtrate was discarded. Then the Sep-Pak© was washed with water/acetonitrile/ trifluoroacetic acid 64.9:35:0.1 (4 mL) and the filtrate was diluted with water (11 mL) and lyophilized to 4 mg of the title product.

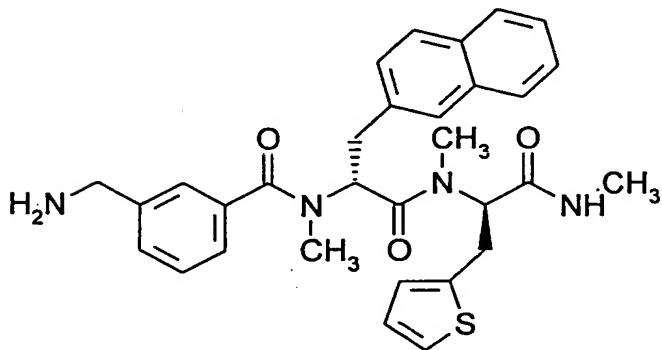
HPLC:(A1) R_t = 31.05 min

(B1) R_t = 33.00 min

s LC-MS: 557.0 ($m+1$)[†]

Example 77

3-Aminomethyl-N-methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(methylcarbamoyl)-
10 2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide:



The title compound was prepared analogously to example 76 with 3-(1-(tert-
15 butoxycarbonylamino)methyl)-benzoic acid instead of 3-(1-(tert-butoxy-
carbonylamino)ethyl)benzoic acid.

Yield: 5.0 mg

20 HPLC:(A1) R_t = 30.32 min

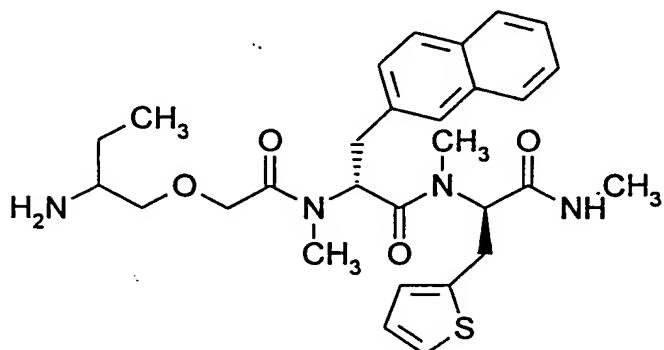
(B1) R_t = 32.22 min

LC-MS: 542.8 ($m+1$)[†]

Example 78

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide:

5



The title compound was prepared analogously to example 76 with (2-(tert-butoxycarbonylamino)butoxy)- acetic acid instead of 3-(1-(tert-butoxycarbonylamino)ethyl)benzoic acid.

Yield: 10.4 mg

HPLC:(A1) $R_t = 30.13$ min

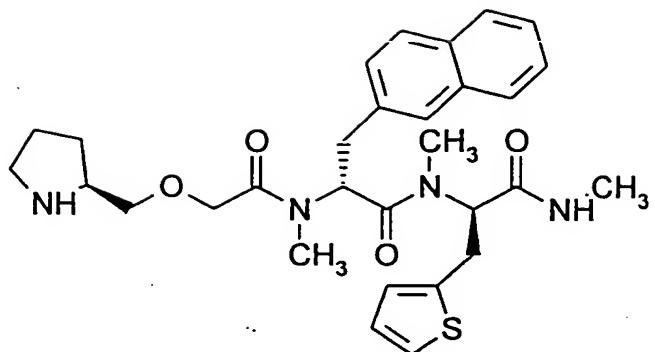
15 (B1) $R_t = 31.98$ min

LC-MS: $(m+1)^+$

Example 79

20

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide:



The title compound was prepared analogously to example 76 with (2S)-2-((carboxy)methoxy)methyl)pyrro-lidin-1-carboxylic acid tert-butyl ester

5 instead of 3-(1-(tert-butoxy-carbonylamino)ethyl)benzoic acid.

Yield: 9.4 mg

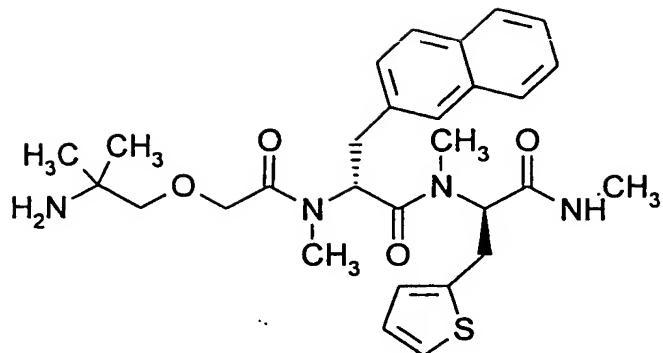
HPLC:(A1) $R_t = 30.07$ min

10 (B1) $R_t = 31.88$ min

LC-MS: $(m+1)^+$

15 Example 80

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide:



The title compound was prepared analogously to example 76 with (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid instead of 3-(1-(tert-butoxycarbonylamino)ethyl)benzoic acid.

Yield: 10.5 mg

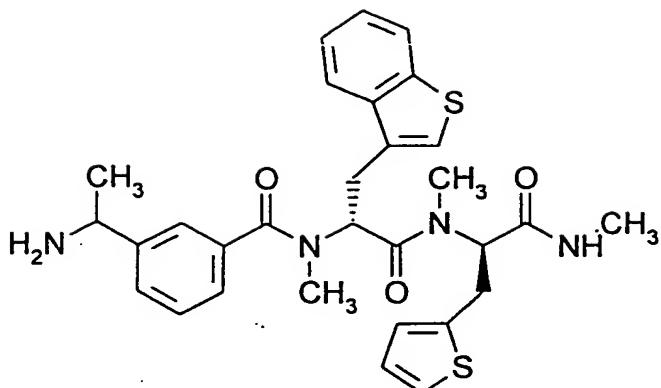
HPLC:(A1) $R_t = 29.77$ min

(B1) $R_t = 31.62$ min

LC-MS: $(m+1)^+$

15 Example 81

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide:



The title compound was prepared analogously to example 76 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-5-methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 3.2 mg

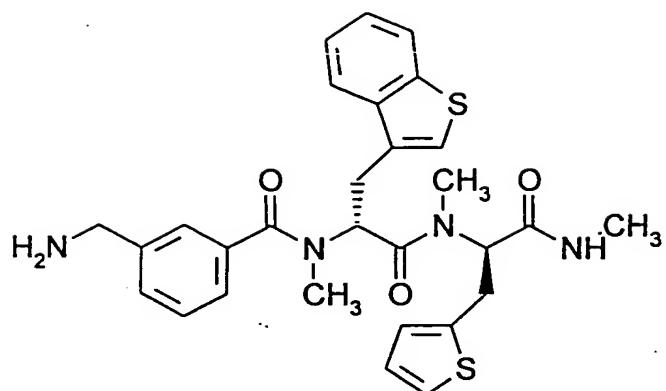
10 HPLC:(A1) $R_t = 30.62$ min
(B1) $R_t = 32.57$ min

LC-MS: 563.0 ($m+1$)⁺

15

Example 82

3-(1-Aminomethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide:



The title compound was prepared analogously to example 77 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl))-N-methylamino-propionic acid instead of 2-(N-(9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino-3-(2-naphthyl)propionic acid.

Yield: 2.0 mg

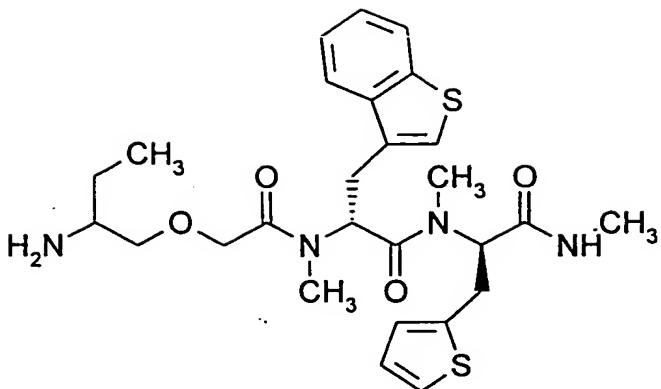
10 HPLC: (A1) $R_t = 29.82$ min
 (B1) $R_t = 31.73$ min

LC-MS: 549.0 ($m+1$)⁺

15

Example 83

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 78 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-propionic acid instead of 2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: mg

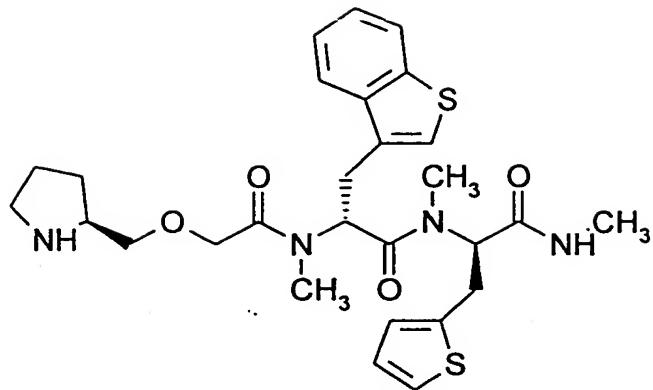
10 HPLC: (A1) R_t = min
 (B1) R_t = min

LC-MS: ($m+1$)⁺

15

Example 84

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 79 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 7.6 mg

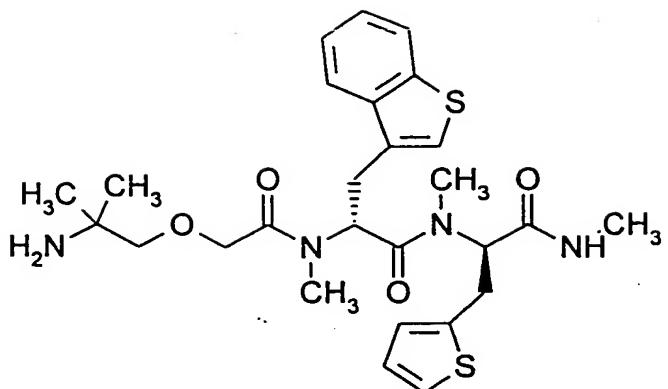
10 HPLC:(A1) $R_t = 29.42$ min

(B1) $R_t = 31.23$ min

LC-MS: 557.0 ($m+1$)^{*}

15 Example 85

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 80 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl))-N-
 5 methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-
 yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 5.8 mg

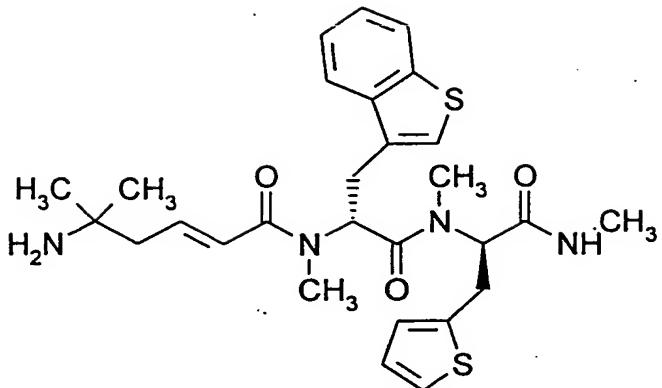
10 HPLC:(A1) $R_t = 29.22$ min
 (B1) $R_t = 31.00$ min

LC-MS: 544.8 ($m+1$)⁺

15

Example 86

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-
 20 (benzo[b]thiophen-3-yl)ethyl)amide:



The title compound was prepared analogously to example 85 with (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 2.0 mg

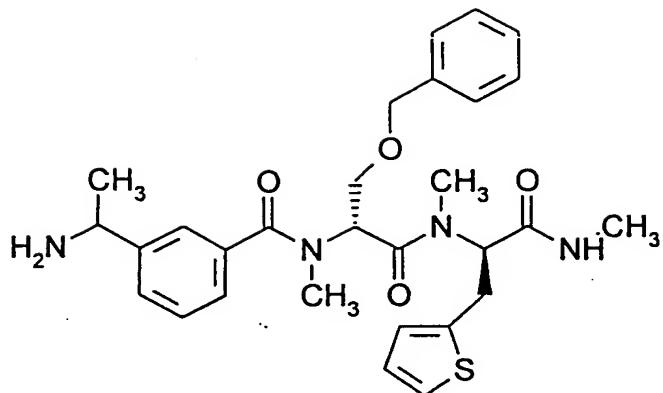
HPLC:(A1) $R_t = 29.62$ min

10 (B1) $R_t = 31.50$ min

LC-MS: 541.2 ($m+1$)⁺

15 Example 87

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-2-((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 10.0 mg

10 HPLC:(A1) $R_t = 28.85$ min

(B1) $R_t = 30.67$ min

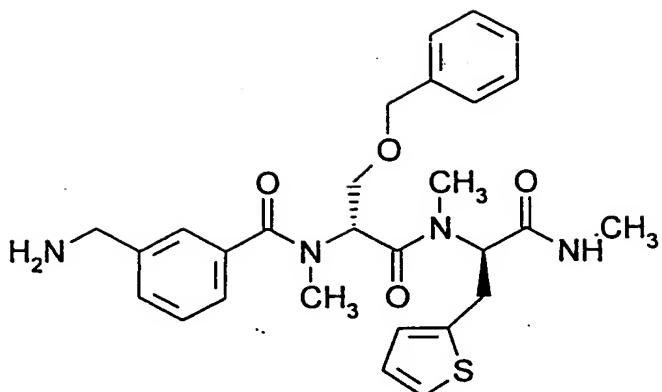
LC-MS: $(m+1)^+$

15

Example 88

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:

20



The title compound was prepared analogously to example 77 with (2R)-2-((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)-3-benzyloxypropionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 8.4 mg

HPLC: (A1) $R_t = 30.45$ min
 (B1) $R_t = 30.43$ min

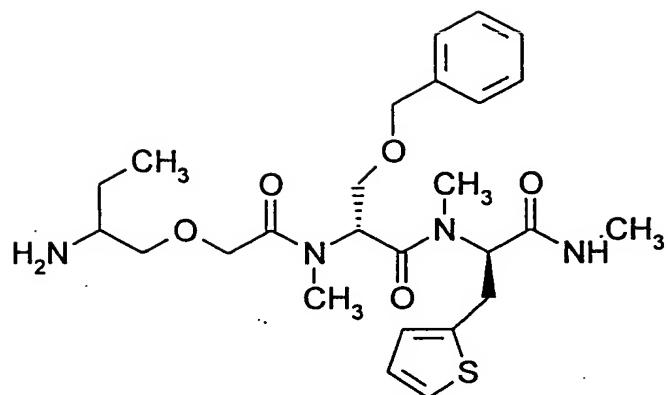
LC-MS: 522.8 ($m+1$)⁺

15

Example 89

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 78 with (2R)-2-((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)-3-benzyloxypropionic
 5 acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 9.8 mg

10 HPLC:(A1) R_t = min
 (B1) R_t = min

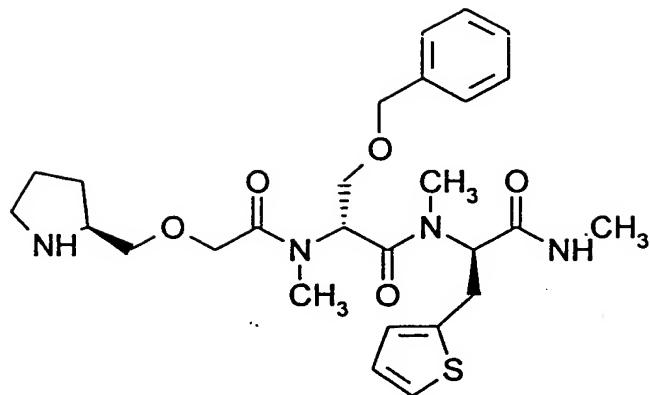
LC-MS: 519.0 ($m+1$)⁺

15

Example 90

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 79 with (2R)-2-((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 11.1 mg

10 HPLC:(A1) $R_t = 27.77$ min

(B1) $R_t = 29.40$ min

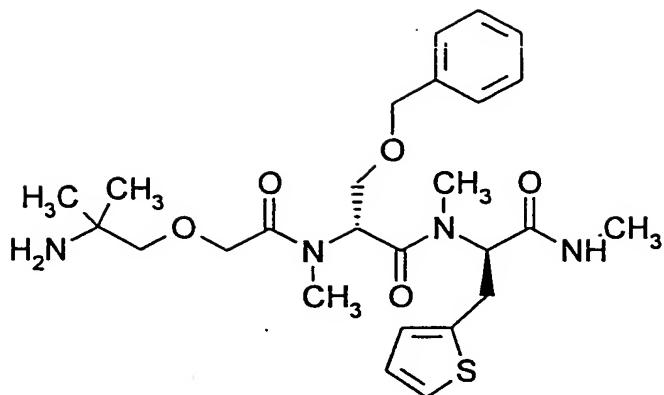
LC-MS: $(m+1)^+$

15

Example 91

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 80 with (2R)-2-((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 11.9 mg

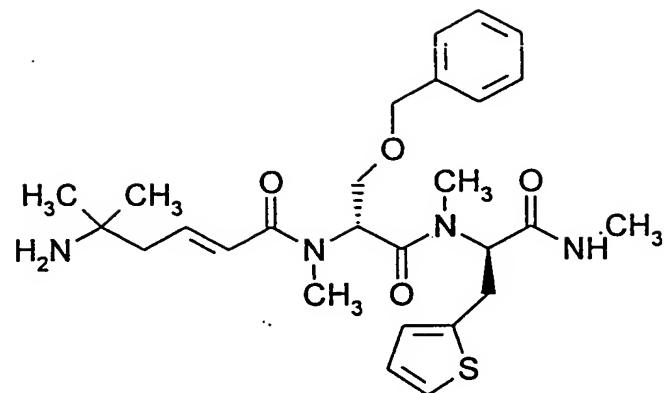
10 HPLC:(A1) $R_t = 28.50$ min

(B1) $R_t = 29.23$ min

LC-MS: 519.0 ($m+1$)⁺

15 Example 92

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide:



The title compound was prepared analogously to example 91 with (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 1.5 mg

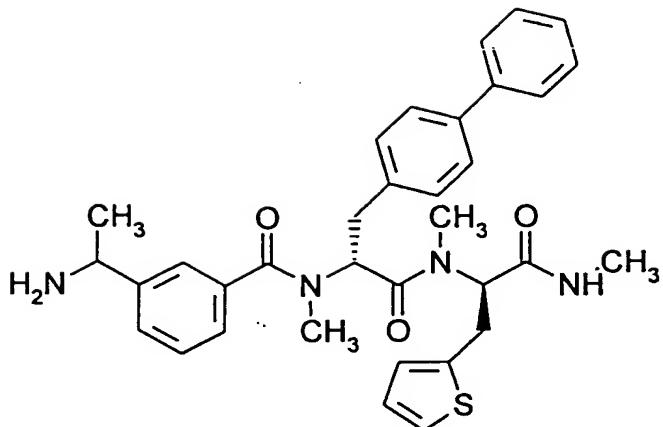
HPLC:(A1) $R_t = 28.03$ min

10 (B1) $R_t = 29.77$ min

LC-MS: $(m+1)^+$

15 Example 93

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-

5 methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

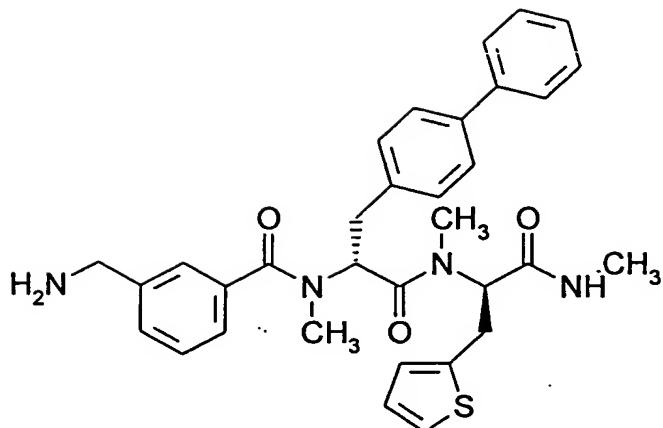
Yield: 2.0 mg

10 HPLC:(A1) $R_t = 34.58$ min
 (B1) $R_t = 36.67$ min

LC-MS: $(m+1)^+$

15 Example 94

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:



The title compound was prepared analogously to example 77 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 12.3 mg

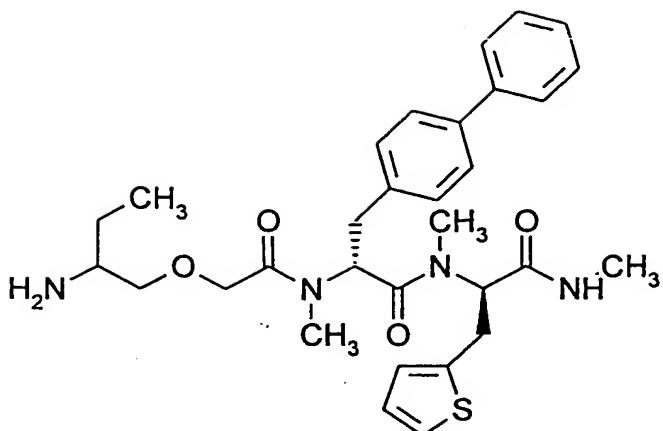
10 HPLC:(A1) R_t = 33.92 min

(B1) R_t = 35.97 min

LC-MS: (m+1)⁺

15 Example 95

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 78 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 13.5 mg

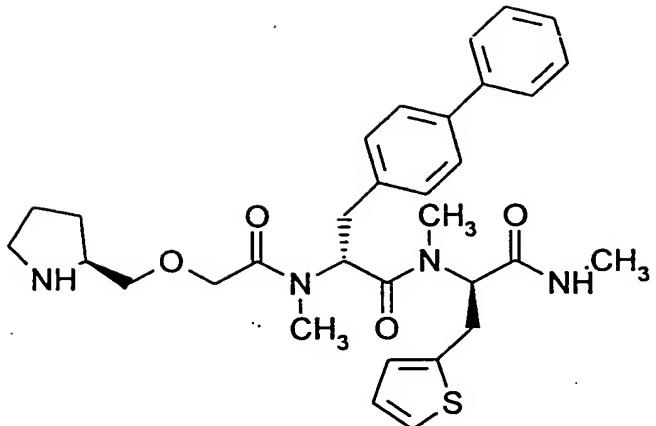
HPLC:(A1) $R_t = 33.57$ min
(B1) $R_t = 34.47$ min

LC-MS: $(m+1)^+$

15

Example 96

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 79 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

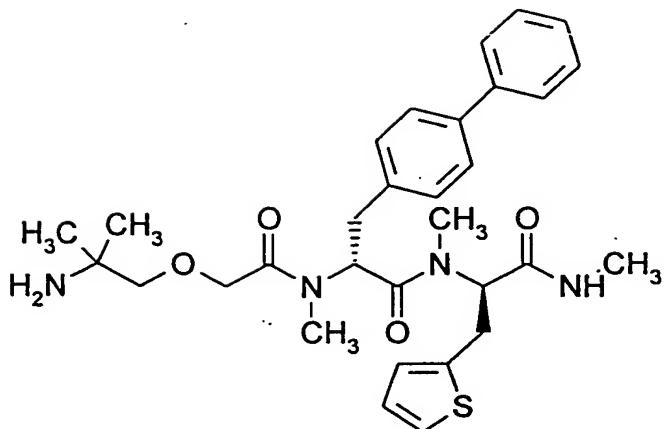
Yield: 11.0 mg

10 HPLC:(A1) R_t = 33.30 min
 (B1) R_t = 35.24 min

LC-MS: ($m+1$)⁺

15 Example 97

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 80 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 13.1 mg

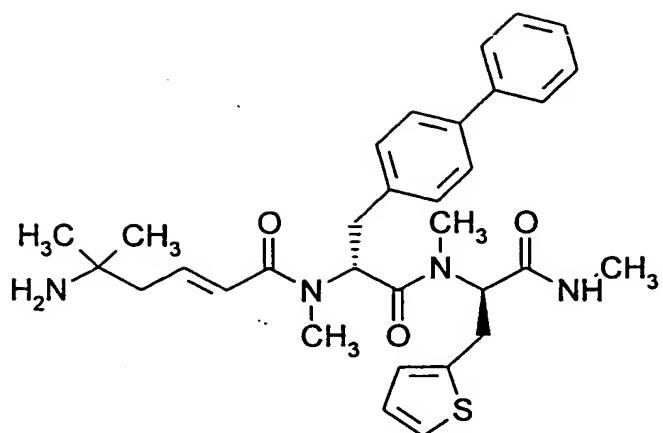
10 HPLC:(A1) $R_t = 27.68$ min
(B1) $R_t = 30.22$ min

LC-MS: $(m+1)^+$

15

Example 98

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide:



The title compound was prepared analogously to example 97 with (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-
5) butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 13.1 mg

HPLC:(A1) $R_t = 28.48$ min

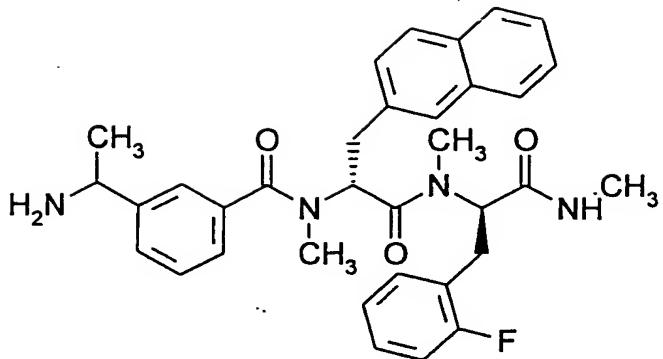
10 (B1) $R_t = 30.03$ min

LC-MS: $(m+1)^+$

15

Example 99

20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(2-
naphthyl)ethyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 5.0 mg

10

HPLC:(A1) R_t = 32.00 min

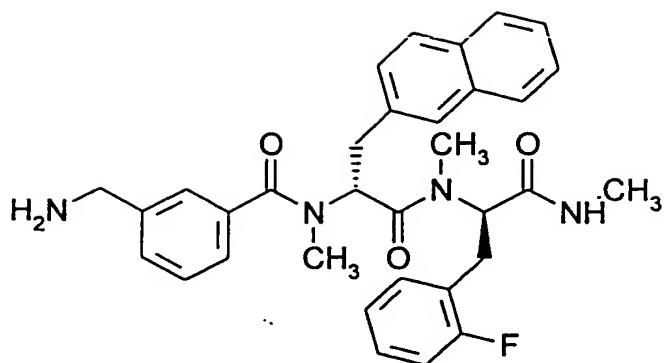
(B1) R_t = 33.98 min

LC-MS: 568.8 ($m+1$)⁺

15

Example 100

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
20 2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide:



The title compound was prepared analogously to example 77 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-

5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 2.8 mg

10

HPLC:(A1) $R_t = 31.30$ min

(B1) $R_t = 33.23$ min

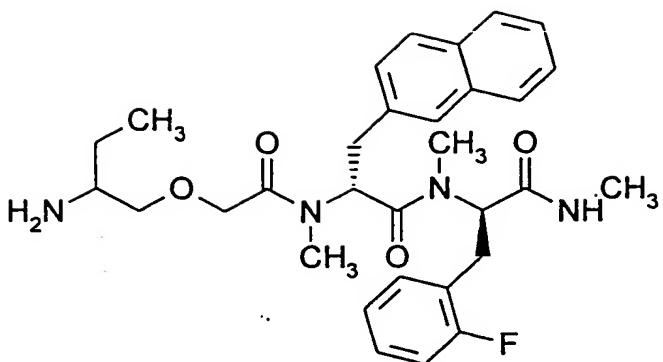
LC-MS: 555.0 ($m+1$)⁺

15

Example 101

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide:

20



The title compound was prepared analogously to example 78 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 10.1 mg

10

HPLC:(A1) $R_t = 31.25$ min

(B1) $R_t = 33.03$ min

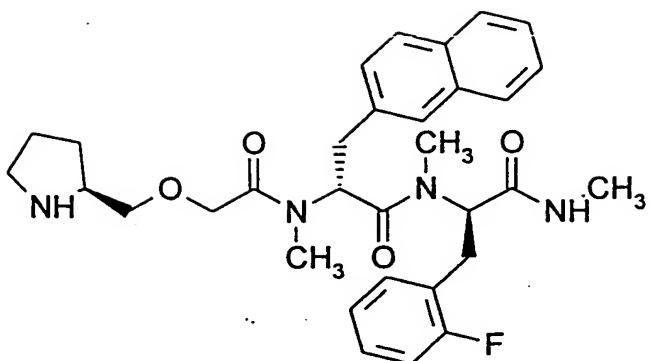
LC-MS: $(m+1)^+$

15

Example 102

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propion-

20 amide:



The title compound was prepared analogously to example 79 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 12.0 mg

10

HPLC:(A1) R_t = 31.90 min

(B1) R_t = 32.73 min

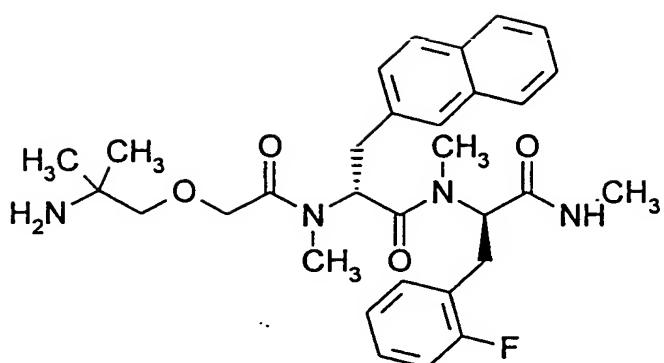
LC-MS: 563.0 (m+1)⁺

15

Example 103

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propion-

20 amide:



The title compound was prepared analogously to example 80 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 11.5 mg

10

HPLC:(A1) $R_t = 30.83$ min

(B1) $R_t = 32.63$ min

LC-MS: 551.0 ($m+1$)⁺

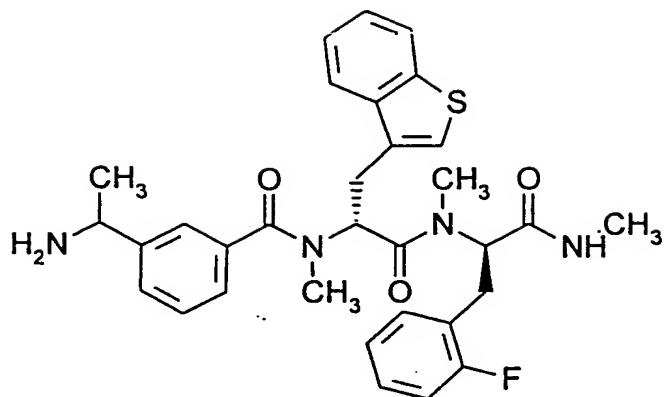
15

Example 104

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-

(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-

20 3-yl)ethyl)-benzamide:



The title compound was prepared analogously to example 81 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 3.6 mg

10

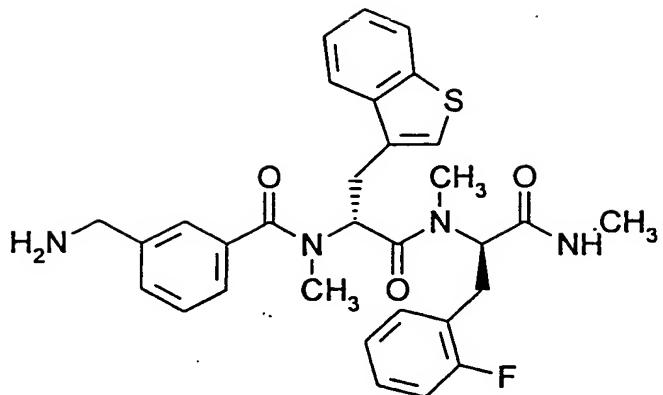
HPLC:(A1) $R_t = 31.60$ min
 (B1) $R_t = 33.57$ min

LC-MS: 575.0 ($m+1$)⁺

15

Example 105

20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benz-
 amide:



The title compound was prepared analogously to example 82 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-5-propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 3.3 mg

10

HPLC:(A1) $R_t = 30.82$ min

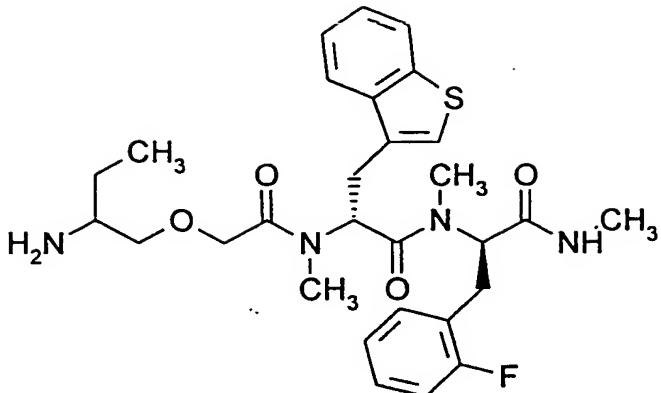
(B1) $R_t = 32.77$ min

LC-MS: 561.0 ($m+1$)⁺

15

Example 106

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 83 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-

5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 10.5 mg

10

HPLC:(A1) R_t = 30.62 min

(B1) R_t = 32.45 min

LC-MS: 557.0 ($m+1$)[†]

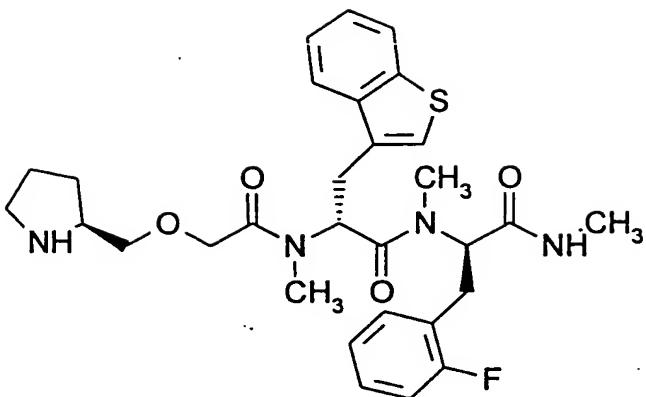
15

Example 107

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-

N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-

20 yl)propionamide:



The title compound was prepared analogously to example 84 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 7.0 mg

10

HPLC:(A1) $R_t = 30.47$ min

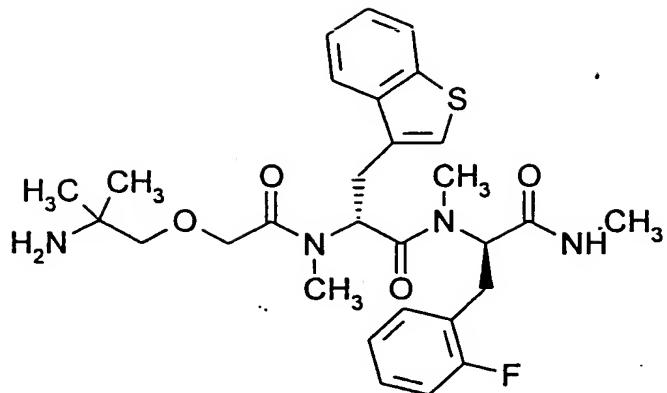
(B1) $R_t = 32.30$ min

LC-MS: 569.0 ($m+1$)⁺

15

Example 108

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
20 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-
yl)propionamide:



The title compound was prepared analogously to example 85 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
methylamino)-3-(2-thienyl)propionic acid.

Yield: 7.5 mg

10

HPLC:(A1) $R_t = 30.33$ min

(B1) $R_t = 32.10$ min

LC-MS: 557.0 ($m+1$)⁺

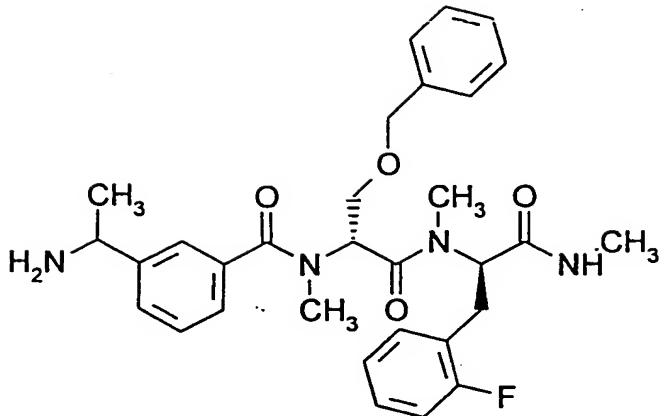
15

Example 109

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-

(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-

20 (benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 87 with (2R)-2-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
methylamino)-3-(2-thienyl)propionic acid.

Yield: 4.6 mg

10

HPLC:(A1) $R_t = 31.07$ min

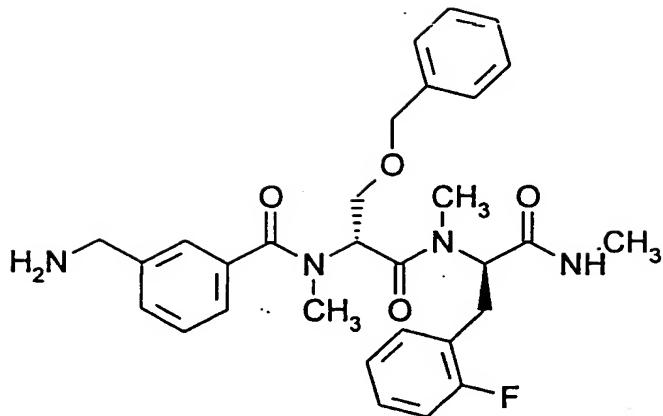
(B1) $R_t = 32.97$ min

LC-MS: 549.0 ($m+1$)⁺

15

Example 110

20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 88 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 5.2 mg

10

HPLC:(A1) R_t = 30.25 min

(B1) R_t = 32.10 min

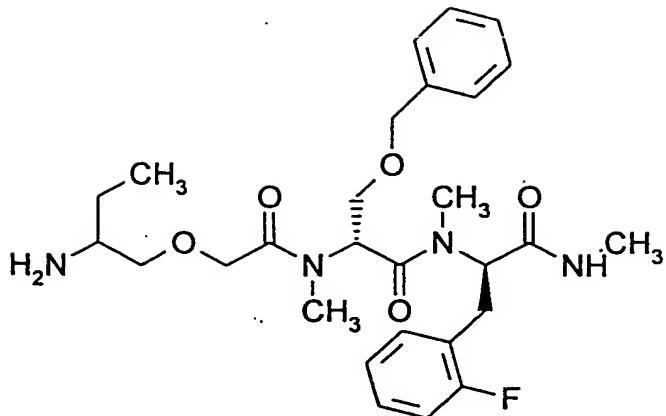
LC-MS: 535.2 ($m+1$)⁺

15

Example 111

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 89 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 23.6 mg

10

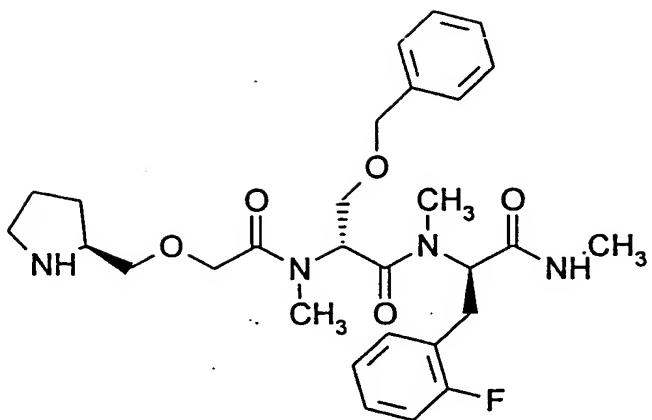
HPLC:(A1) $R_t = 29.32$ min
 (B1) $R_t = 30.97$ min

LC-MS: $(m+1)^+$

15

Example 112

20 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 90 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 26.0 mg

10

HPLC:(A1) R_t = min

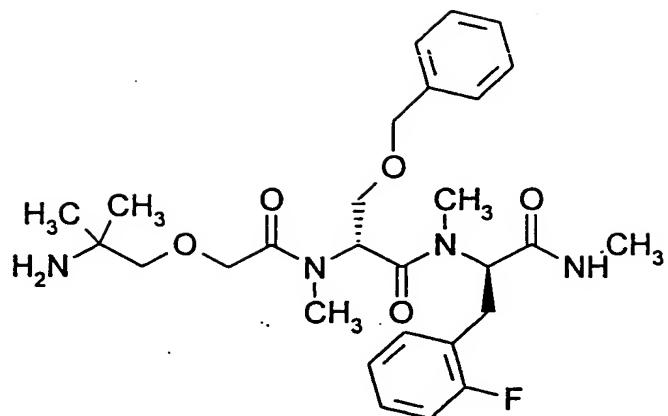
(B1) R_t = min

LC-MS: 543.2 ($m+1$)⁺

15

Example 113

20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-
(benzyloxy)propionamide:



The title compound was prepared analogously to example 91 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 20.1 mg

10

HPLC:(A1) $R_t = 30.17$ min

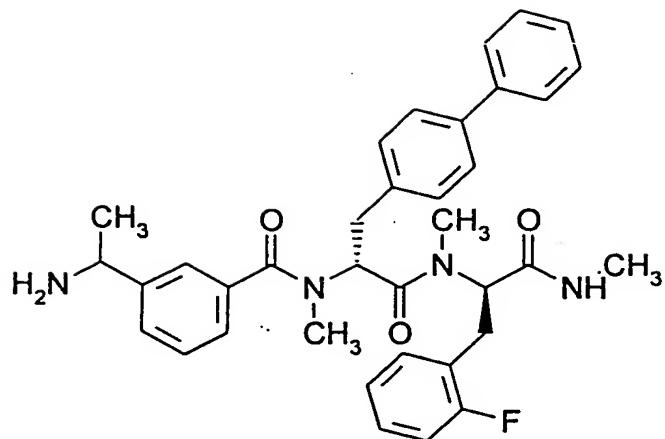
(B1) $R_t = 30.77$ min

LC-MS: 531.0 ($m+1$)⁺

15

Example 114

20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:



The title compound was prepared analogously to example 93 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 10.0 mg

10

HPLC:(A1) $R_t = 35.40$ min

(B1) $R_t = 37.58$ min

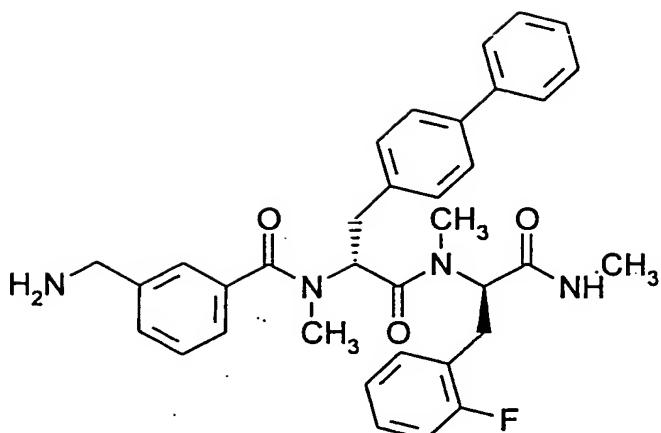
LC-MS: 594.8 ($m+1$)⁺

15

Example 115

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 94 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 6.6 mg

10

HPLC:(A1) R_t = 34.70 min

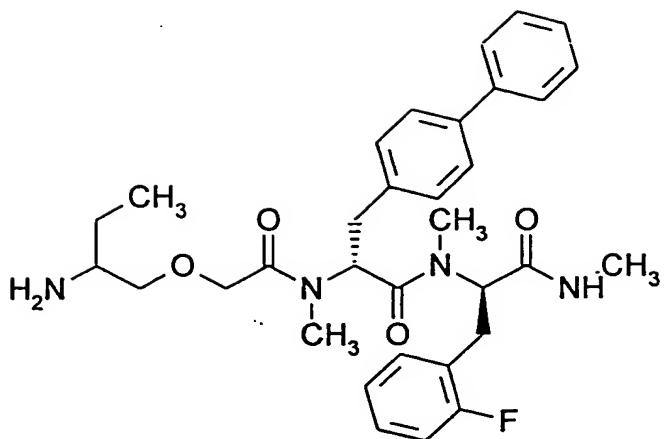
(B1) R_t = 36.08 min

LC-MS: 581.0 ($m+1$)⁺

15

Example 116

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 95 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 23.3 mg

10

HPLC:(A1) $R_t = 34.13$ min

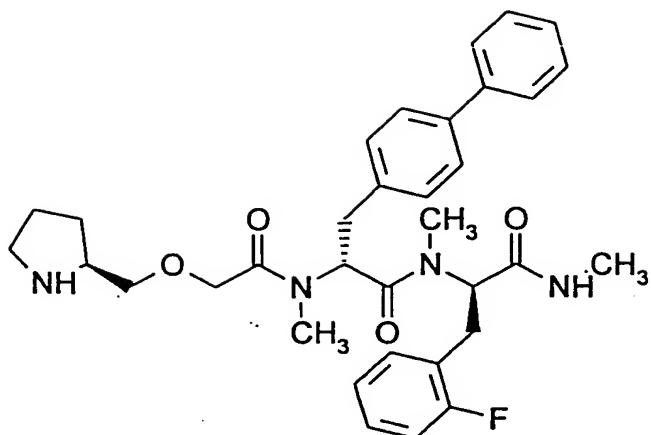
(B1) $R_t = 36.08$ min

LC-MS: $(m+1)^+$

15

Example 117

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-
20 yl)propionamide:



The title compound was prepared analogously to example 96 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 20.5 mg

10

HPLC:(A1) $R_t = 27.65$ min

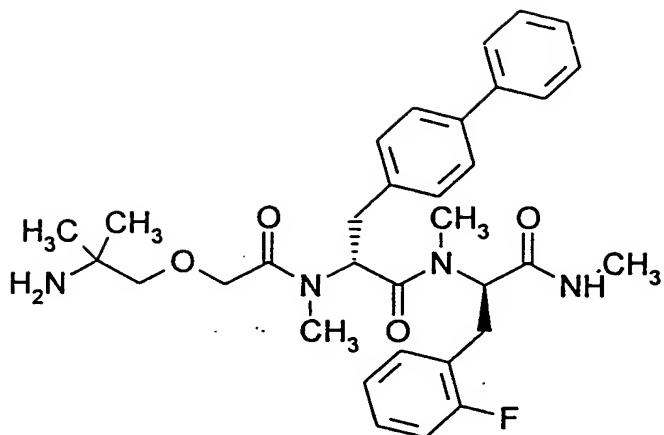
(B1) $R_t = 30.18$ min

LC-MS: $(m+1)^+$

15

Example 118

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
20 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-
yl)propionamide:



The title compound was prepared analogously to example 97 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 12.2 mg

10

HPLC:(A1) $R_t = 34.32$ min

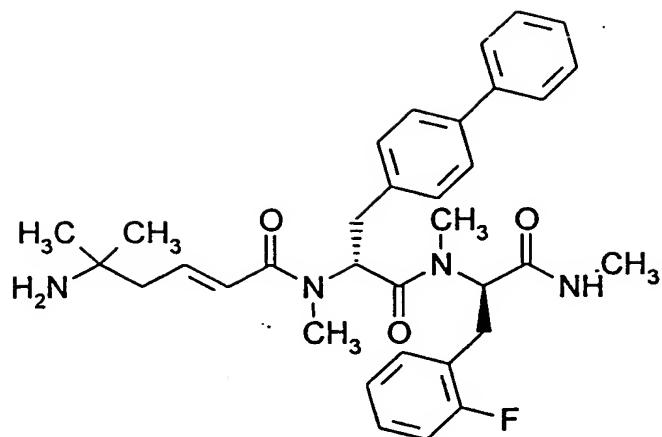
(B1) $R_t = 36.13$ min

LC-MS: 577.0 ($m+1$)⁺

15

Example 119

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(biphenyl-4-
20 yl)ethyl)amide:



The title compound was prepared analogously to example 98 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 5.1 mg

10

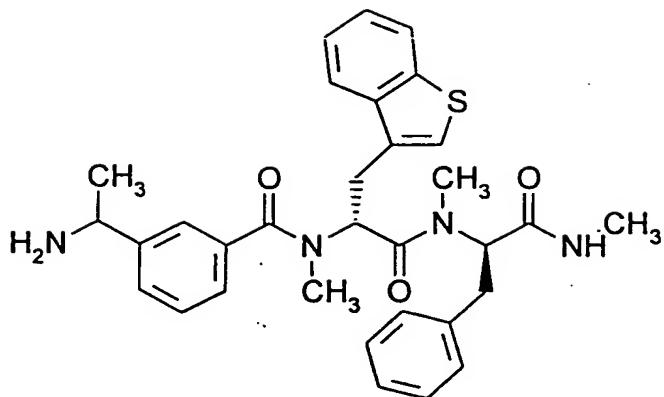
HPLC:(A1) $R_t = 27.68$ min
(B1) $R_t = 30.20$ min

LC-MS: $(m+1)^+$

15

Example 120

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-
yl)ethyl)benzamide:



The title compound was prepared analogously to example 81 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 4.6 mg

10

HPLC:(A1) R_t = min

(B1) R_t = min

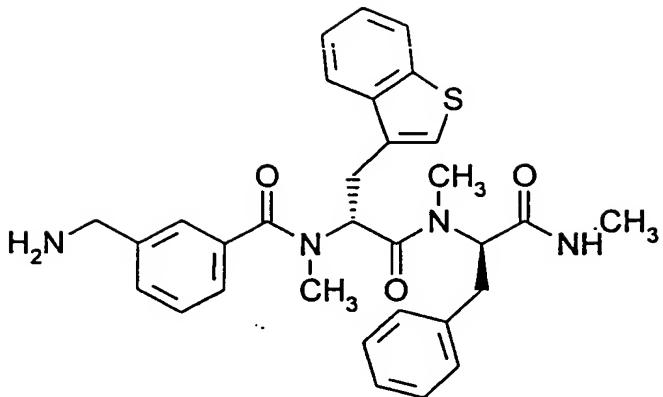
LC-MS: 557.0 ($m+1$)⁺

15

Example 121

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 82 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 3.1 mg

10

HPLC:(A1) R_t = min

(B1) R_t = min

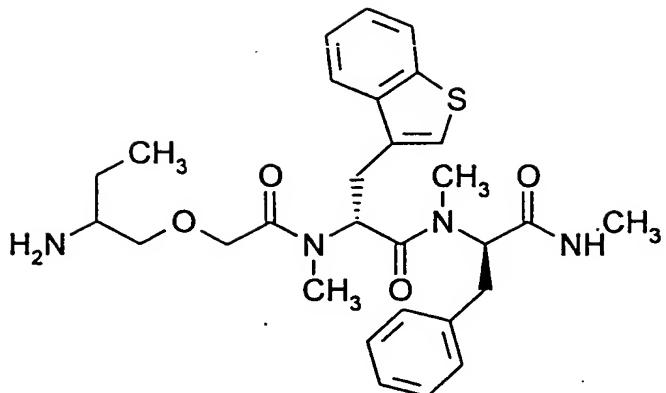
LC-MS: 542.8 ($m+1$)⁺

15

Example 122

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide:

20



The title compound was prepared analogously to example 83 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 1.2 mg

10

HPLC:(A1) $R_t = 30.48$ min

(B1) $R_t =$ min

LC-MS: 539.2 ($m+1$)^{*}

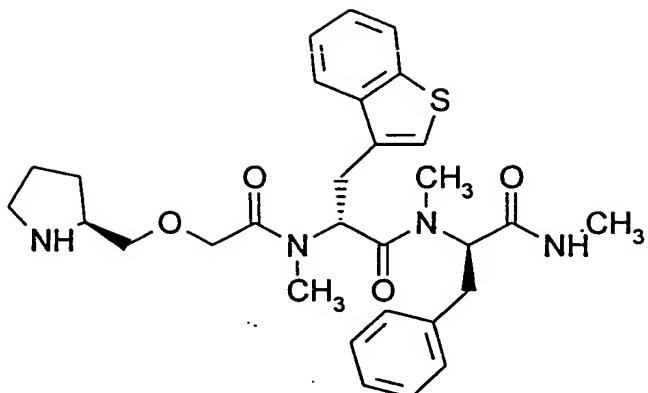
15

Example 123

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-

N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-

20 yl)propion-amide:



The title compound was prepared analogously to example 84 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 2.9 mg

10

HPLC:(A1) $R_t = 30.47$ min

(B1) $R_t =$ min

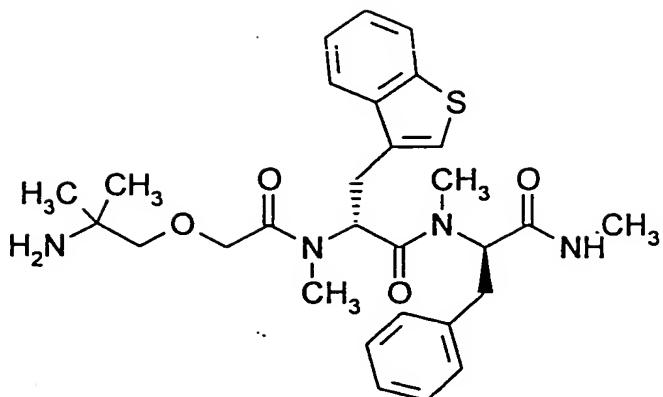
LC-MS: 550.8 ($m+1$)⁺

15

Example 124

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-

20 yl)propionamide:



The title compound was prepared analogously to example 85 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid

5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 3.3 mg

10

HPLC:(A1) $R_t = 30.18 \text{ min}$

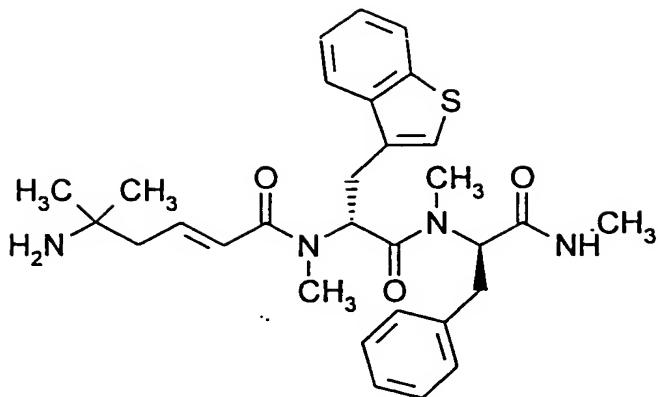
(B1) $R_t = \text{min}$

LC-MS: 539.2 ($m+1$)⁺

15

Example 125

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide:



The title compound was prepared analogously to example 86 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 1.1 mg

10

HPLC:(A1) $R_t = 30.57$ min

(B1) $R_t = \text{min}$

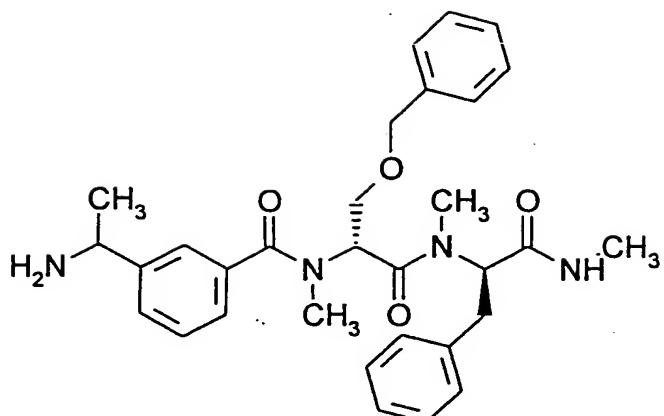
LC-MS: 535.2 ($m+1$)^{*}

15

Example 126

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:

20



The title compound was prepared analogously to example 87 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 15.9 mg

10

HPLC:(A1) $R_t = 30.87$ min
(B1) $R_t = 32.50$ min

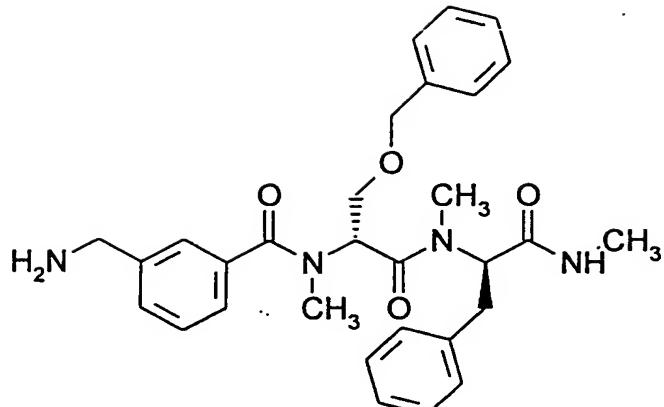
LC-MS: 531.2 ($m+1$)⁺

15

Example 127

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:

20



The title compound was prepared analogously to example 88 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 13.2 mg

10

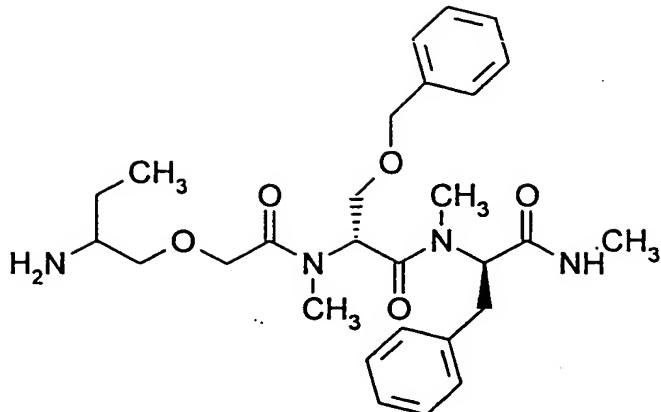
HPLC:(A1) R_t = 30.02 min
(B1) R_t = 31.65 min

LC-MS: 517.0 (m+1)⁺

15

Example 128

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 89 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 14.7 mg

10

HPLC:(A1) $R_t = 29.38$ min
 (B1) $R_t = 30.85$ min

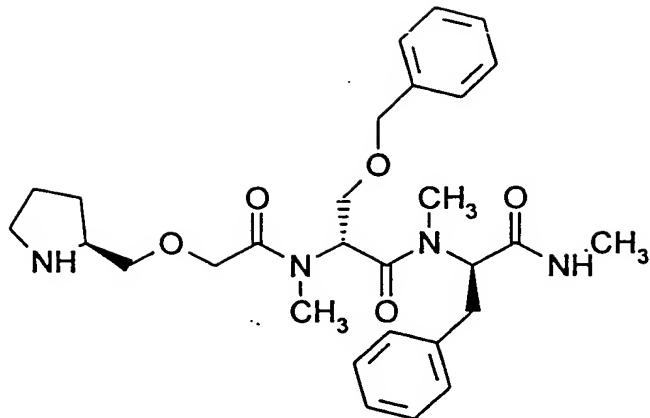
LC-MS: 513.2 ($m+1$)⁺

15

Example 129

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 90 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid

s instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 17.9 mg

10

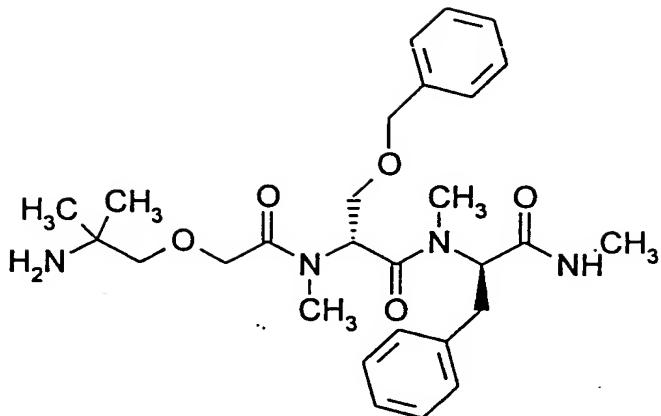
HPLC:(A1) $R_t = 29.00$ min
(B1) $R_t = 30.45$ min

LC-MS: 525.0 ($m+1$)⁺

15

Example 130

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
20 ((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 91 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid

5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 16.5 mg

10

HPLC:(A1) $R_t = 29.15$ min

(B1) $R_t = 30.57$ min

LC-MS: 513.2 ($m+1$)⁺

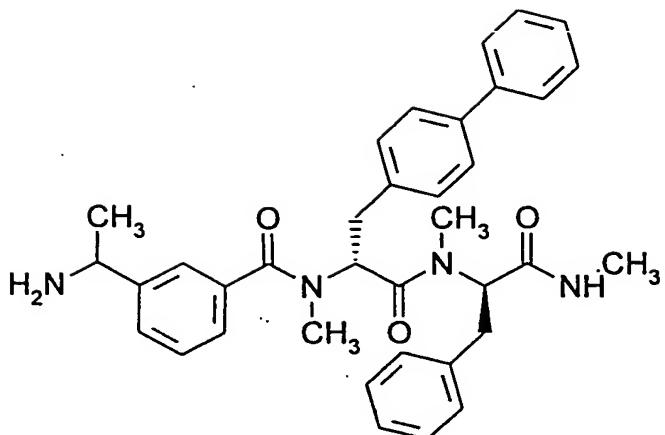
15

Example 131

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-

(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-

20 yl)ethyl)benzamide:



The title compound was prepared analogously to example 93 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid

5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 7.5 mg

10

HPLC:(A1) $R_t = 34.63$ min

(B1) $R_t = \text{min}$

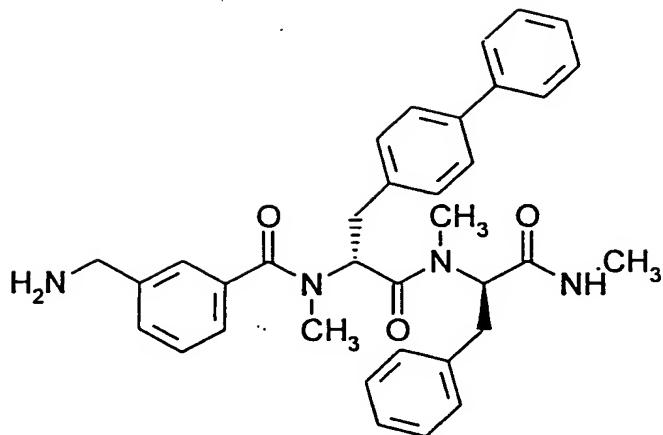
LC-MS: $(m+1)^+$

15

Example 132

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 94 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 9.5 mg

10

HPLC:(A1) $R_t = 35.25$ min
 (B1) $R_t = 36.93$ min

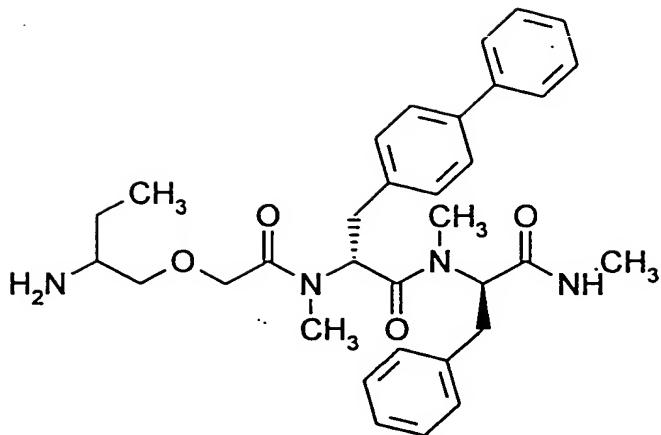
LC-MS: $(m+1)^+$

15

Example 133

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 95 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid

instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 13.3 mg

10

HPLC: (A1) $R_t = 34.30$ min

(B1) $R_t = 36.10$ min

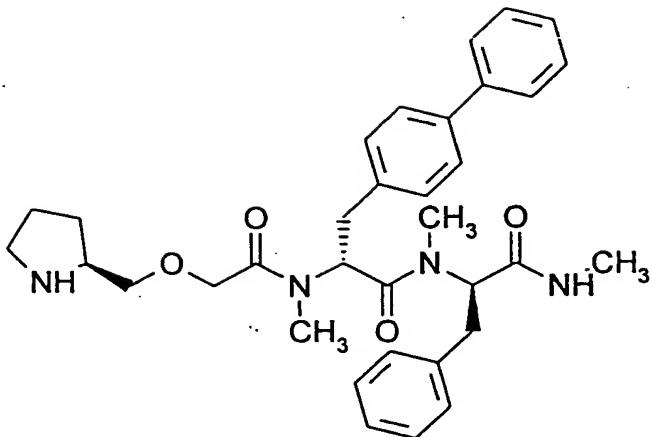
LC-MS: 559.0 ($m+1$)⁺

15

Example 134

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 96 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid

5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 20.9 mg

10

HPLC:(A1) $R_t = 34.47$ min

(B1) $R_t = 36.17$ min

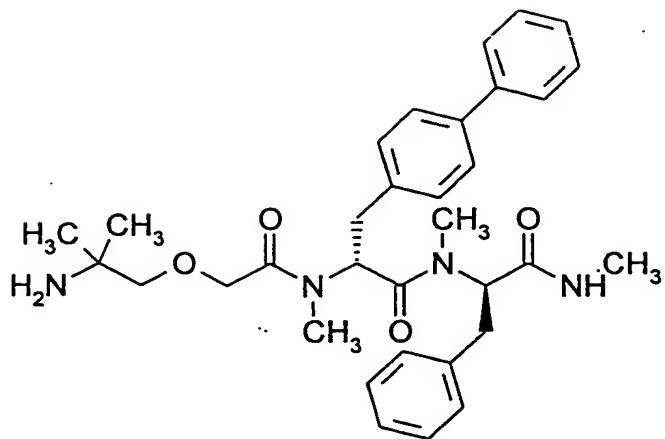
LC-MS: 571.0 ($m+1$)⁺

15

Example 135

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 97 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 25.4 mg

10

HPLC:(A1) $R_t = 34.05$ min

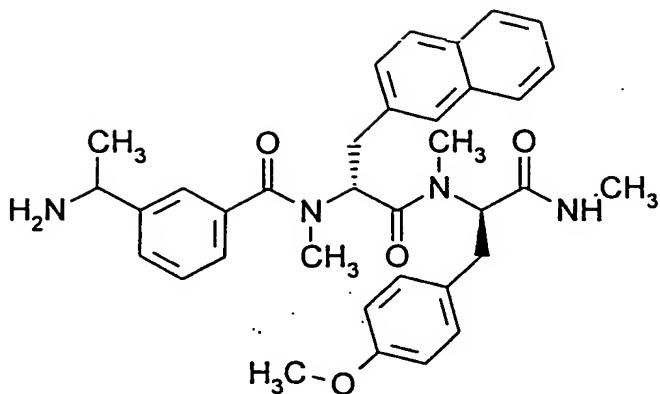
(B1) $R_t = 35.78$ min

LC-MS: 559.0 ($m+1$)⁺

15

Example 136

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 8.3 mg

10

HPLC:(A1) R_t = 31.32 min

(B1) R_t = 32.92 min

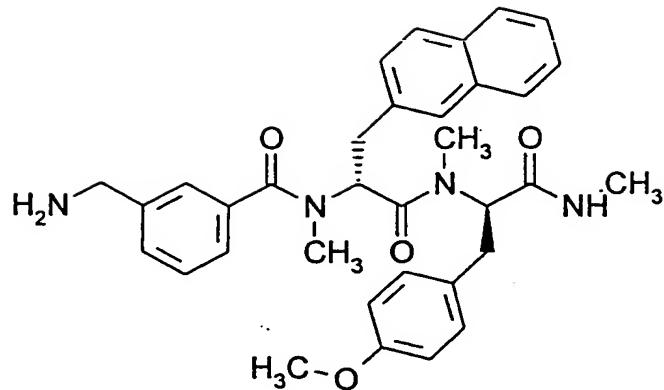
LC-MS: 580.8 (m+1)⁺

15

Example 137

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide:

20



The title compound was prepared analogously to example 77 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 4.1 mg

10

HPLC:(A1) $R_t = 30.62$ min

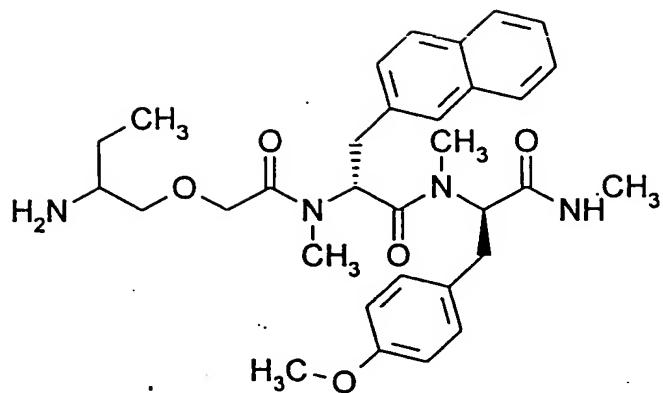
(B1) $R_t = \text{min}$

LC-MS: 566.8 ($m+1$)⁺

15

Example 138

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide:



The title compound was prepared analogously to example 78 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 18.0 mg

10

HPLC:(A1) $R_t = 30.78$ min

(B1) $R_t = 32.27$ min

LC-MS: 563.2 ($m+1$)⁺

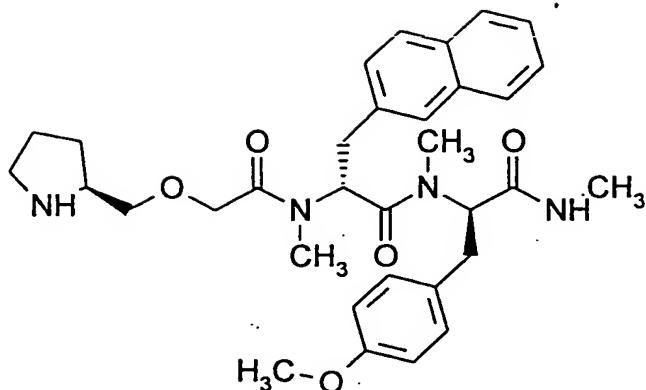
15

Example 139

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino-N-methyl-

N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)-

20 propionamide:



The title compound was prepared analogously to example 79 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 24.0 mg

10

HPLC:(A1) $R_t = 30.85$ min

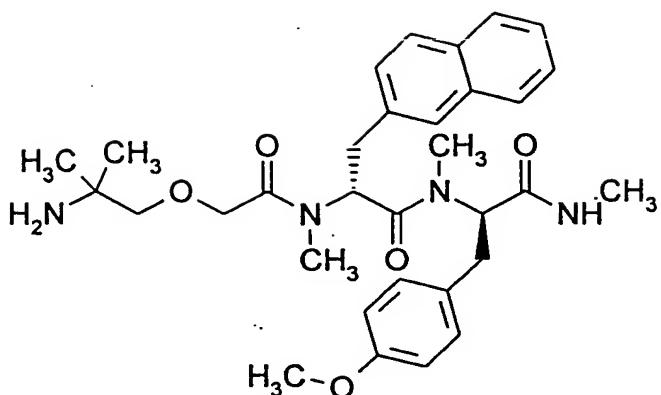
(B1) $R_t = 32.40$ min

LC-MS: 574.8 ($m+1$)⁺

15

Example 140

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propion-
amide:



The title compound was prepared analogously to example 80 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
methylamino)-3-(2-thienyl)-propionic acid.

Yield: 15.6 mg

10

HPLC:(A1) $R_t = 30.37$ min

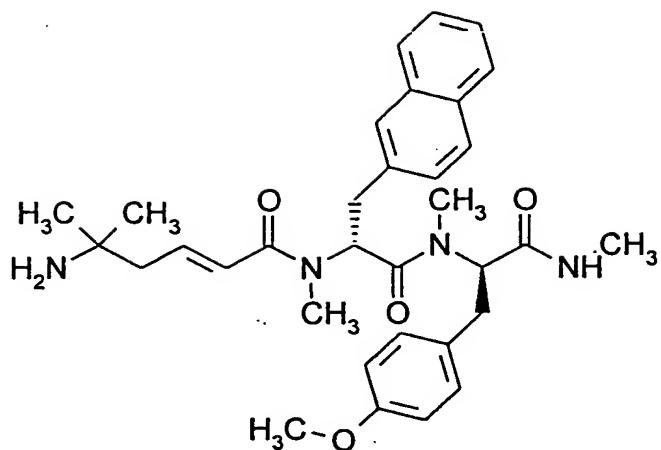
(B1) $R_t = 31.90$ min

LC-MS: 563.2 ($m+1$)^{*}

15

Example 141

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-
20 naphthyl)-ethyl)amide:



The title compound was prepared analogously to example 140 with (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 2.9 mg

HPLC:(A1) R_t = min

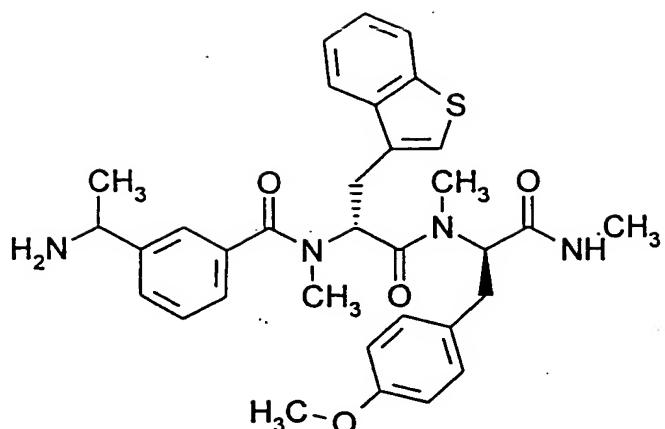
(B1) R_t = min

LC-MS: 559.0 ($m+1$)⁺

Example 142

15

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide:



The title compound was prepared analogously to example 81 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 3.4 mg

10

HPLC:(A1) R_t = 30.90 min

(B1) R_t = min

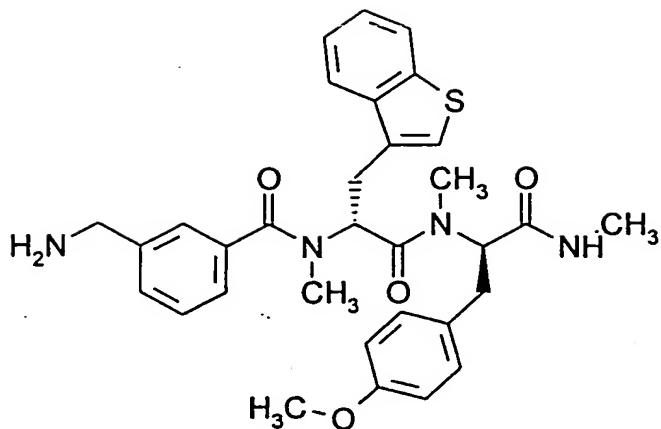
LC-MS: 586.8 ($m+1$)⁺

15

Example 143

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-

20 benzamide:



The title compound was prepared analogously to example 82 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
methylamino)-3-(2-thienyl)-propionic acid.

Yield: 5.5 mg

10

HPLC:(A1) $R_t = 30.15$ min

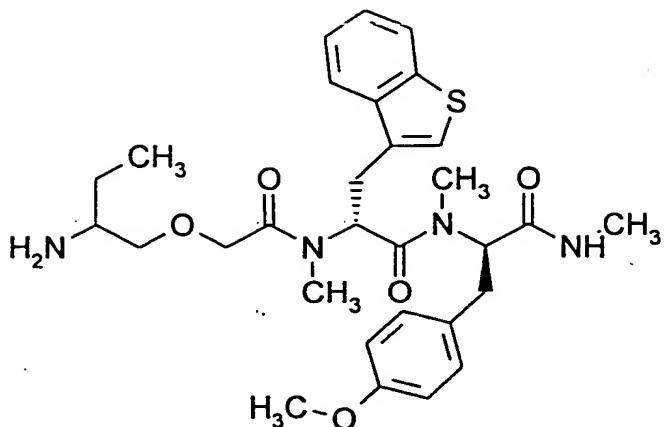
(B1) $R_t = \text{min}$

LC-MS: 573.0 ($m+1$)⁺

15

Example 144

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-
yl)propionamide:



The title compound was prepared analogously to example 83 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 7.5 mg

10

HPLC:(A1) $R_t = 30.18$ min

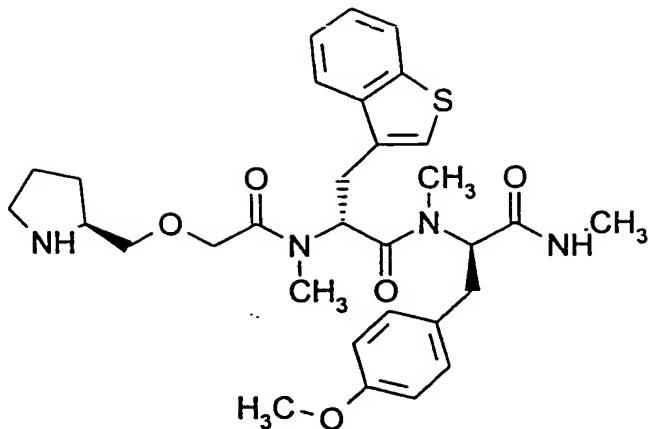
(B1) $R_t = \text{min}$

LC-MS: 569.0 ($m+1$)^{*}

15

Example 145

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-
20 (benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 84 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 10.5 mg

10

HPLC:(A1) R_t = 30.20 min

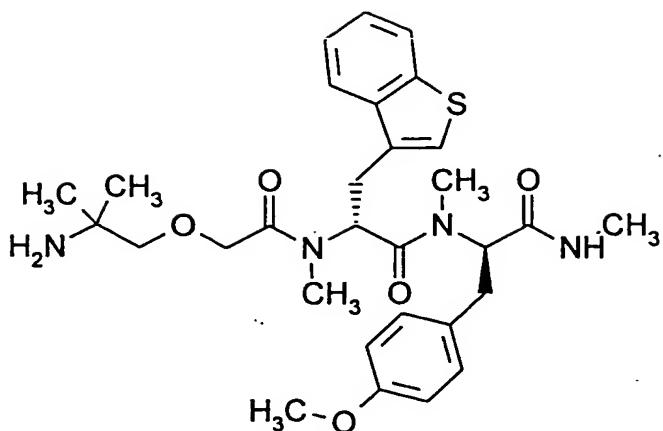
(B1) R_t = min

LC-MS: 581.0 ($m+1$)⁺

15

Example 146

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 85 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 s propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 9.9 mg

10

HPLC:(A1) R_t = 29.87 min

(B1) R_t = min

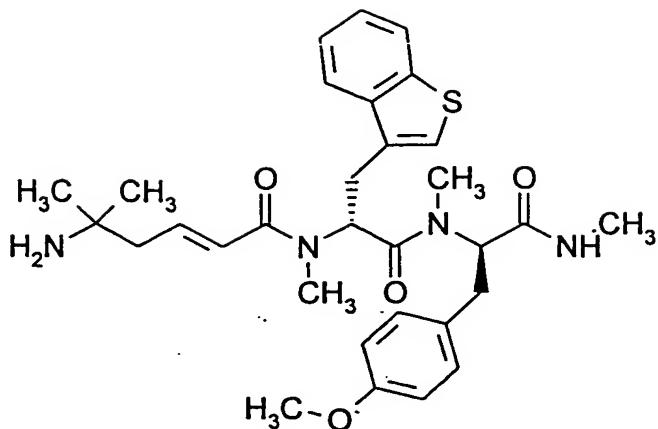
LC-MS: 569.0 ($m+1$)⁺

15

Example 147

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-

20 (benzo[b]thiophen-3-yl)ethyl)amide:



The title compound was prepared analogously to example 86 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-5-propionic acid instead of (2R)-2-(N-(9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 4.0 mg

10

HPLC:(A1) R_t = 30.42 min

(B1) R_t = min

LC-MS: $(m+1)^+$

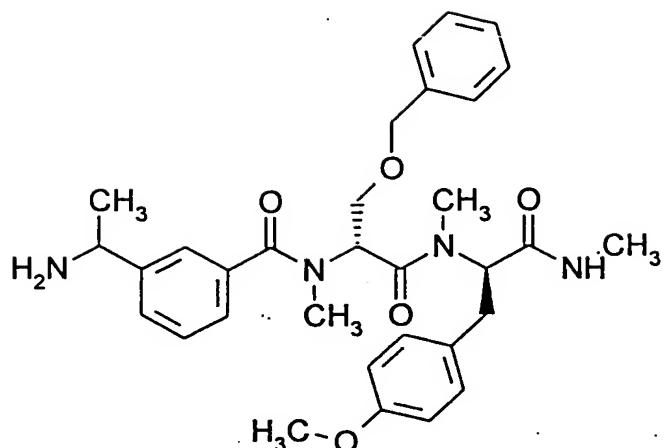
15

Example 148

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-

(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-

20 (benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 87 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 6.1 mg

10

HPLC:(A1) $R_t = 30.82$ min

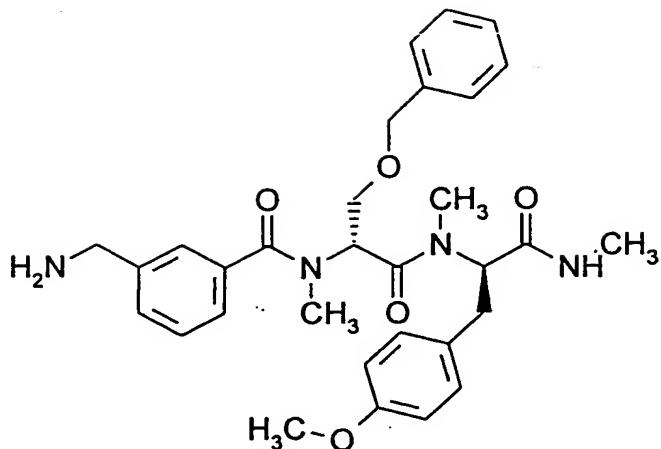
(B1) $R_t = \text{min}$

LC-MS: 561.2 ($m+1$)⁺

15

Example 149

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
20 2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 88 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-

5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 7.3 mg

10

HPLC:(A1) R_t = 36.23 min

(B1) R_t = min

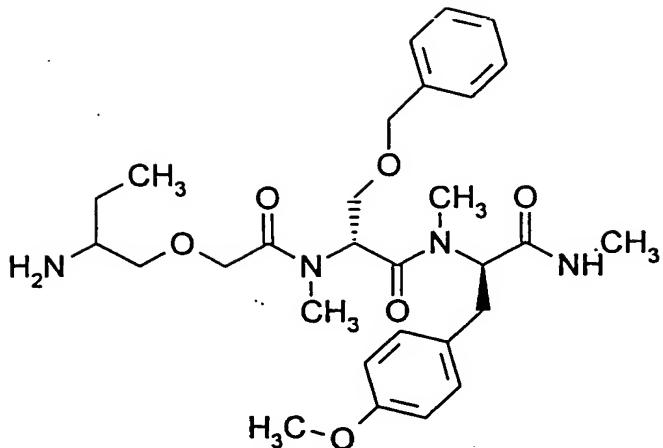
LC-MS: 547.0 ($m+1$)⁺

15

Example 150

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-

20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 89 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 s propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 2.4 mg

10

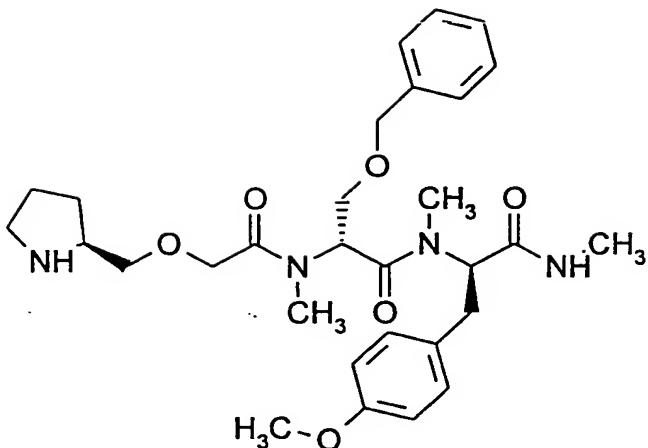
HPLC:(A1) R_t = min
 (B1) R_t = min

LC-MS: $(m+1)^+$

15

Example 151

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 20 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-
 (benzyloxy)propionamide:



The title compound was prepared analogously to example 90 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-

5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 19.0 mg

10

HPLC:(A1) $R_t = 28.65$ min

(B1) $R_t = 30.02$ min

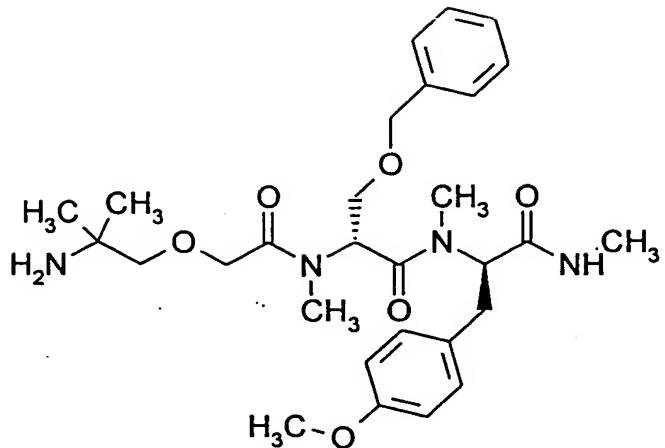
LC-MS: 555.0 ($m+1$)⁺

15

Example 152

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-

20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 91 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 20.5 mg

10

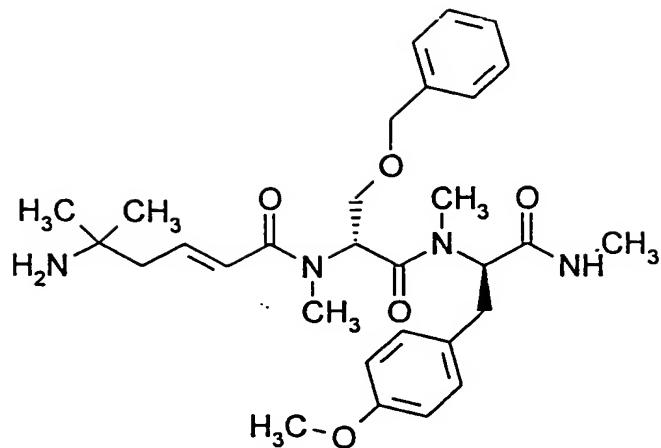
HPLC:(A1) $R_t = 28.80$ min
 (B1) $R_t = 30.17$ min

LC-MS: 543.2 ($m+1$)⁺

15

Example 153

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-
 (benzyloxy)ethyl)amide:



The title compound was prepared analogously to example 92 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 4.0 mg

10

HPLC:(A1) $R_t = 28.37$ min

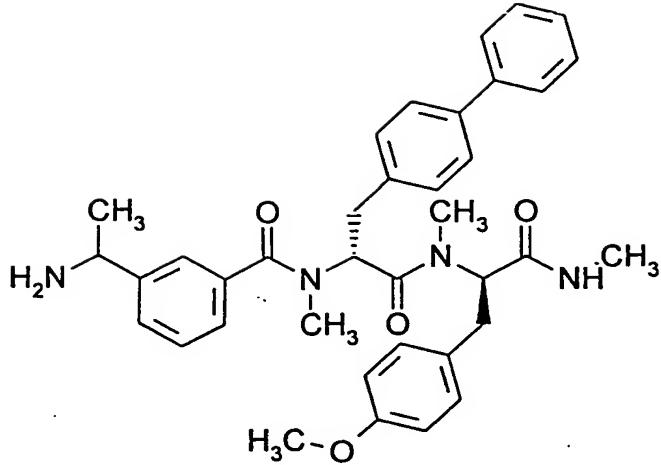
(B1) $R_t =$ min

LC-MS: 539.2 ($m+1$)⁺

15

Example 154

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(biphen-4-
 yl)ethyl)benzamide:



The title compound was prepared analogously to example 93 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 8.2 mg

10

HPLC:(A1) R_t = min

(B1) R_t = min

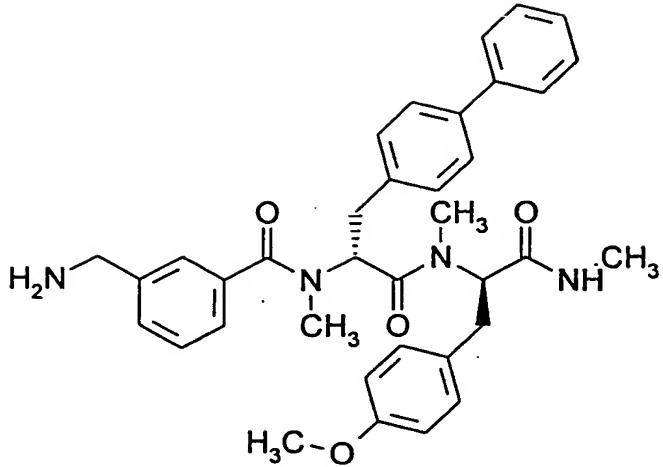
LC-MS: 607.0 (m+1)⁺

15

Example 155

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 94 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 7.2 mg

10

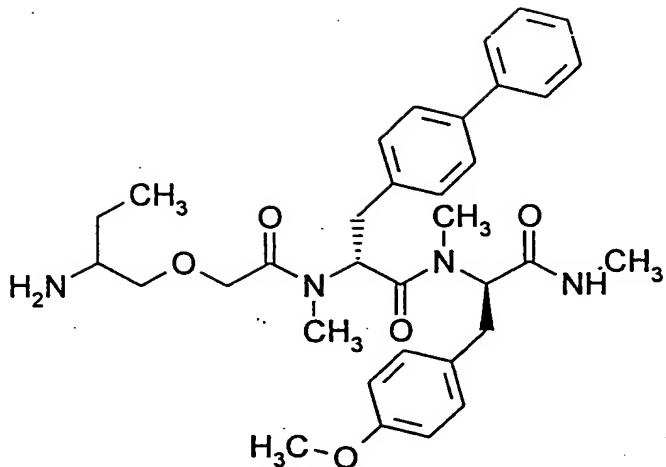
HPLC:(A1) $R_t = \text{min}$
 (B1) $R_t = \text{min}$

LC-MS: 593.2 ($m+1$)⁺

15

Example 156

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-
 20 yl)propionamide:



The title compound was prepared analogously to example 95 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-

5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)-propionic acid.

Yield: 6.0 mg

10

HPLC:(A1) R_t = min

(B1) R_t = min

LC-MS: 589.2 ($m+1$)[†]

15

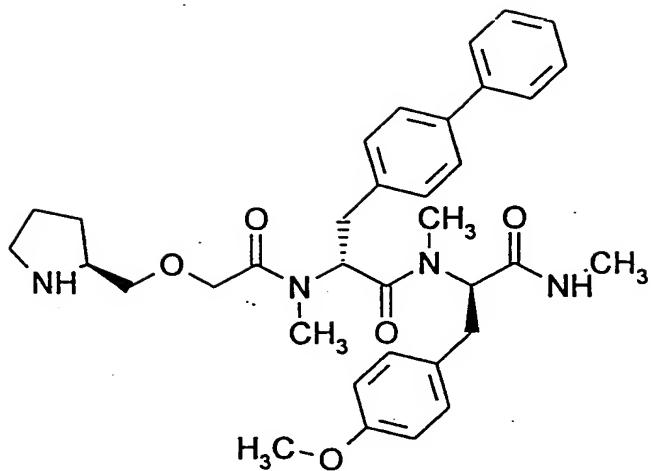
Example 157

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-

N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-

20 yl)propionamide:

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The title compound was prepared analogously to example 96 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
methylamino)-3-(2-thienyl)-propionic acid.

Yield: 10.0 mg

10

HPLC:(A1) R_t = min
(B1) R_t = min

LC-MS: 601.0 ($m+1$)⁺

15

General Procedure for Example 158-533

The following 376 compounds were prepared as single entities by parallel
20 synthesis on a solid support using an Fmoc strategy on an Advanced ChemTech
Model 384 HTS employing HATU/HOAt (O-(7-azabenzotriazol-1-yl)-1,1,3,3-
tetramethyluronium hexafluorophosphate/1-hydroxy-7-azabenzotriazole)
mediated amidecoupling in dimethylformamide (DMF) according to a protocol

known for those skilled in the art.

The compounds were prepared sequentially according to the following equation

Resin—[Building block 1] →

Resin—[Building block 1]—[Building block 2] →

Resin—[Building block 1]—[Building block 2]—[Building block 3] →

Resin—[Building block 1]—[Building block 2]—[Building block 3]—[Building block 4]

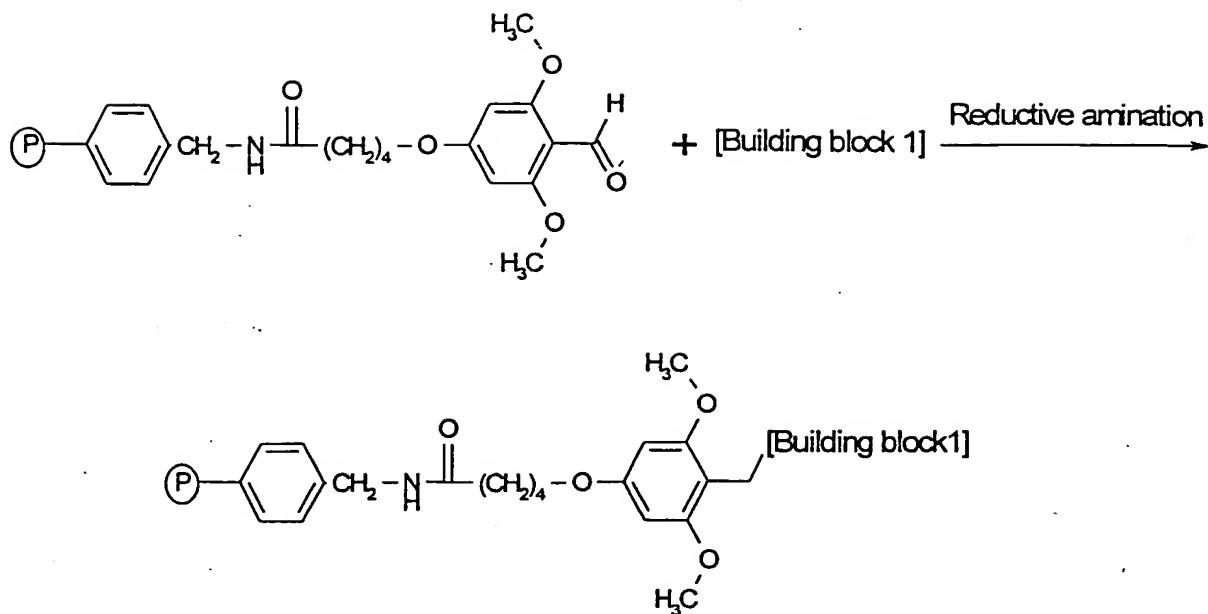
5

and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid (TFA) in dichloromethane (DCM) to give the desired compounds as individual entities according to the following formula

10 [Building block 4]-[Building block 3]-[Building block 2]-[Building block 1].

The starting resins were all prepared separately by reductive amination of [Building block 1] and a 5-(4-formyl-3,5-dimethoxyphenoxy)valerate resin as described in Example 44 for N-Me-PAL.

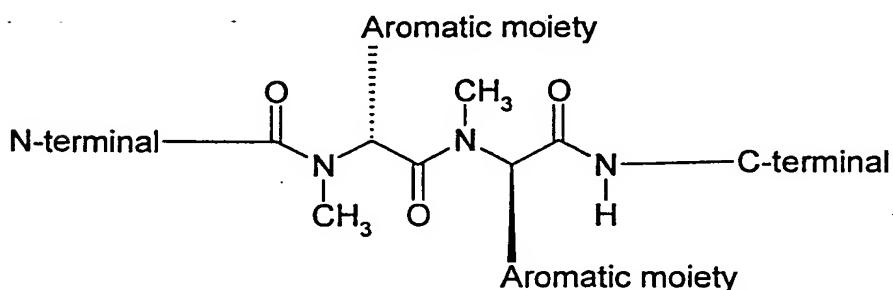
15



The substitution capacities of the resins were 0.5 - 0.7 mmol/g determined by UV monitoring of the deprotection of the Fmoc protection group.

5

All 376 compounds are based on a scaffold and four varying groups according to the following formula, which is included in general formula I:



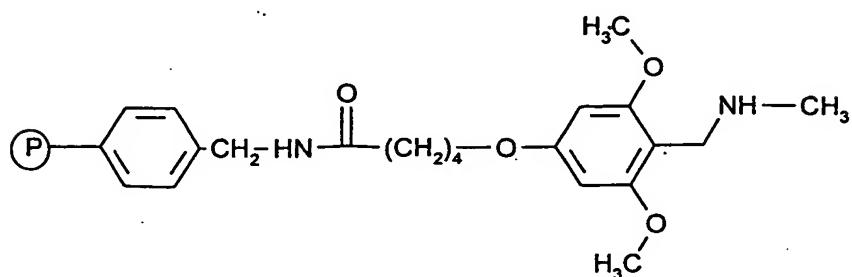
10

The 376 compounds were prepared as three separate libraries based on total combination of four selected building blocks (see example 158-253, example 254-353 and example 354-533) and prepared analogously to the procedure described 15 in Example 158.

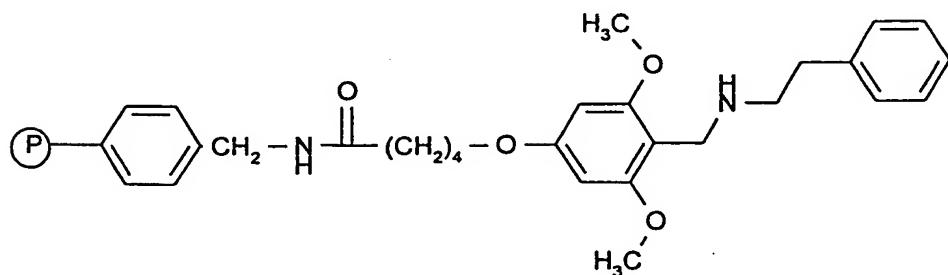
The following resins, here depicted as Resin-[Building block 1] were used:

Resins

5 Name: N-Me-PAL (described in Example 44)

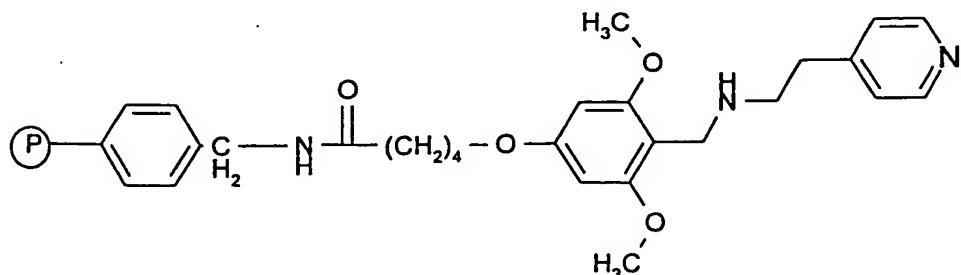


Name: N-Phenethyl-PAL (prepared analogously to N-Me-PAL)



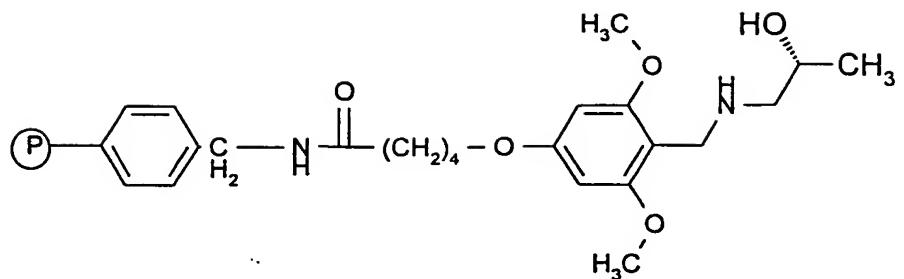
10

Name: N-(4-Pyridyl)ethyl-PAL (prepared analogously to N-Me-PAL)

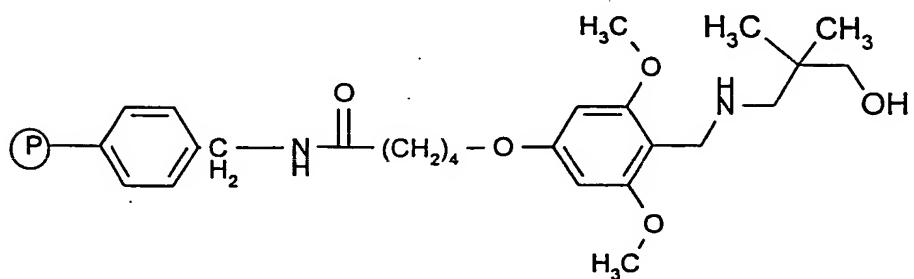


15

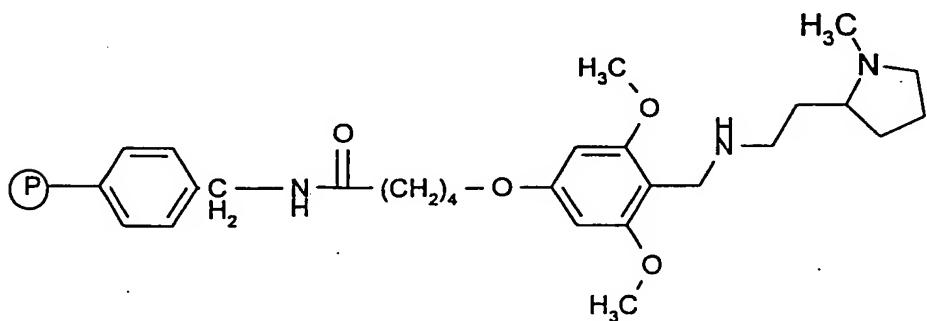
Name: N-((S)-2-Hydroxypropyl)-PAL (prepared analogously to N-Me-PAL)



5 Name: N-(2,2-Dimethyl-3-hydroxypropyl)-PAL (prepared analogously to N-Me-PAL)



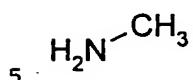
10 Name: N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL (prepared analogously to N-Me-PAL)



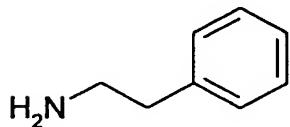
15 The following building blocks were used:

Building block 1

Name: Methylamine

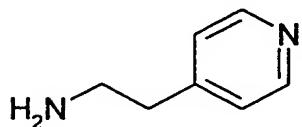


Name: Phenethylamine

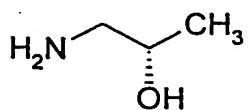


10

Name: 2-(4-pyridyl)ethylamine

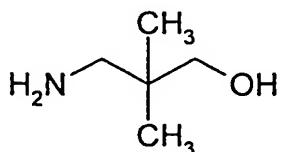


15 Name: (S)-2-Hydroxypropylamine

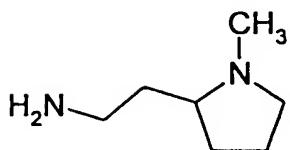


Name: 2,2-Dimethyl-3-hydroxypropylamine

20



Name: 2-(1-Methylpyrrolidine-2-yl)ethylamine

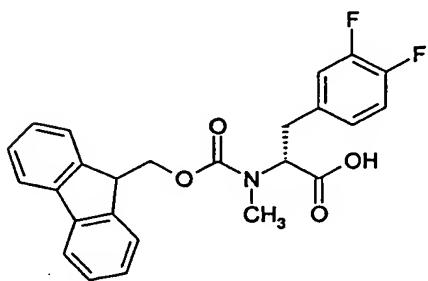


5

Building block 2

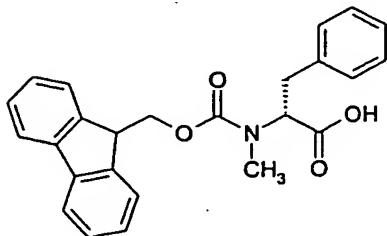
Name: (2R)-2-[N-(9H-Fluoren-9-yl)methoxycarbonyl]-N-methylamino]-3-(3,4-difluorophenyl)propionic acid

10 Abbreviation: Fmoc-N-Me-D-Phe(3,4-F,F)-OH



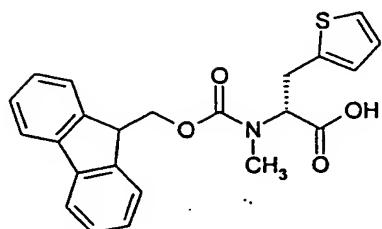
15 Name: (2R)-2-(N-((9H-Flouren-9-yl)methoxy)carbonyl)-N-methylamino)-3-phenylpropionic acid

Abbreviation: Fmoc-N-Me-D-Phe-OH



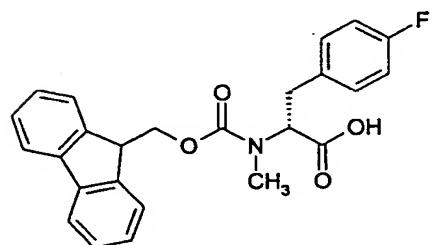
20 Name: (2R)-2-(N-(9H-Fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid

Abbreviation: Fmoc-N-Me-D-ThiAla-OH



5 Name: (2R)-2-[N-(9H-Fluoren-9-yl)methoxycarbonyl]-N-methylamino-3-(4-fluorophenyl)propionic acid

Abbreviation: Fmoc-N-Me-D-Phe(4-F)-OH



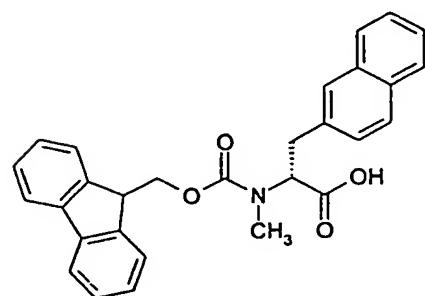
10

Building block 3

Name: (2R)-2-(N-((9H-Flouren-9-yl)methoxy)carbonyl)-N-methylamino-3-(2-

15 naphtyl)propionic acid

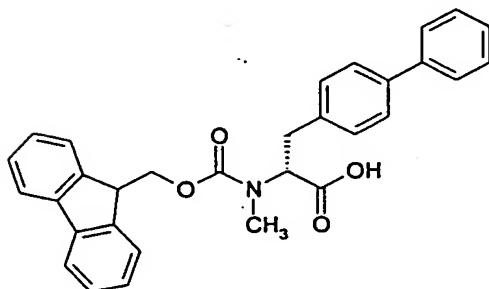
Abbreviation: Fmoc-N-Me-D-2-Nal-OH



Name: (2R)-3-(Biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid

Abbreviation: Fmoc-N-Me-D-Phe(4-Phe)-OH

5



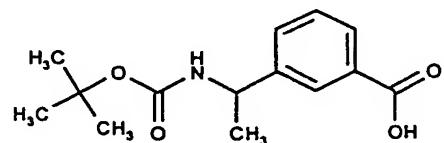
10062695-020102

10 Building block 4

Name: 3-(1-(tert-Butyloxycarbonylamino)ethyl)benzoic acid

Abbreviation: Boc-AEB-OH

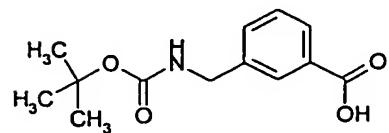
15



Name: 3-(t-Butyloxycarbonylaminomethyl)benzoic acid

Abbreviation: Boc-AMB-OH

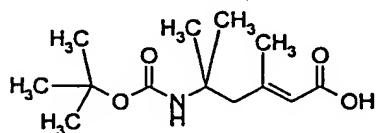
20



Name: (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid

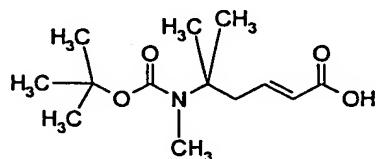
Abbreviation: Boc-ADH-OH

5



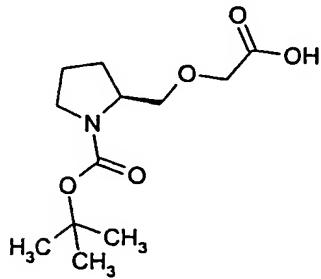
10 Name: (2E)-5-(N-(tert-Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid.

Abbreviation: Boc-MAMH-OH



15 Name: (2S)-2-(((Carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butyl ester

Abbreviation: Boc-SPMA-OH

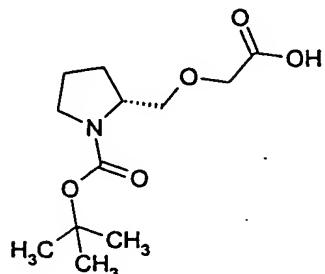


20

Name: (2R)-2-(((Carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butyl

ester

Abbreviation: Boc-RPMA-OH

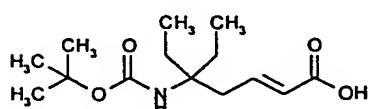


5

Name: (2E) 5-tert-Butoxycarbonylamino-5-ethylhept-2-enoic acid

Abbreviation: Boc-AEHA-OH

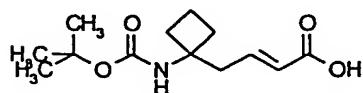
10



15

Name: (2E)-4-(1-(tert-butoxycarbonylamino)cyclobutyl)but-2-enoic acid

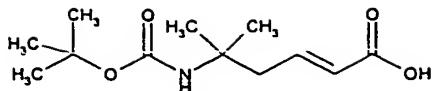
Abbreviation: Boc-ACBB-OH



20

Name: (2E)-5-(tert-butyloxycarbonylamino)-5-methylhex-2-enoic acid

Abbreviation: Boc-AMH-OH



Example 158

5

The N-Me-PAL resin ([building block 1] attached to resin) (0.05 mmol) with a substitution capacity of 0.6 mmol/g was repeatedly (4 times) swelled in dichloromethane and dimethylformamide for 2 min and filtered.

1.0 Coupling: DIEA (0.025 mmol) in DCM (0.034 ml), HATU (0.0125 mmol) in DMF (0.5 ml), a solution of HOAt (0.0125 mmol) and Fmoc-N-Me-D-Phe(4-F)-OH [building block 2] (0.0125 mmol) in DMF (0.5 ml) and DMF (0.5 ml) were added.

The mixture was allowed to shake for 16 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

1.5 Coupling: DIEA (0.00625 mmol) in DCM (0.0085 ml), HATU (0.003125 mmol) in DMF (0.125 ml), a solution of HOAt (0.003125 mmol) and Fmoc-N-Me-D-Phe(4-F)-OH [building block 2] (0.003125 mmol) in DMF (1.25 ml) were added.

The mixture was allowed to shake for 4 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

Deprotection: A solution of 20% piperidine in DMF (1.5 ml) was added and the mixture was shaken for 20 min. The resin was repeatedly (7 times) swelled in dimethylformamide for 90 sec and filtered.

2.0 Coupling: DIEA (0.025 mmol) in DCM (0.034 ml), HATU (0.0125 mmol) in DMF (0.5 ml), a solution of HOAt (0.0125 mmol) and Fmoc-N-Me-D-2-Nal-OH [building block 3] (0.0125 mmol) in DMF (0.5 ml) and DMF (0.5 ml) were added.

The mixture was allowed to shake for 16 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

2.5 Coupling: DIEA (0.00625 mmol) in DCM (0.0085 ml), HATU (0.003125 mmol) in DMF (0.125 ml), a solution of HOAt (0.003125 mmol) Fmoc-N-Me-D-2-Nal-OH [building block 3] (0.003125 mmol) in DMF (1.25 ml) were added. The mixture

was allowed to shake for 4 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

Deprotection: A solution of 20% piperidine in DMF (1.5 ml) was added and the mixture was shaken for 20 min. The resin was repeatedly (7 times) swelled in dimethylformamide for 90 sec and filtered.

3.0 Coupling: DIEA (0.025 mmol) in DCM (0.034 ml), HATU (0.0125 mmol) in DMF (0.5 ml), a solution of HOAt (0.0125 mmol) and Boc-AMH-OH [building block 10 4] (0.0125 mmol) in DMF (0.5 ml) and DMF (0.5 ml) were added. The mixture was allowed to shake for 16 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

3.5 Coupling: DIEA (0.00625 mmol) in DCM (0.0085 ml), HATU (0.003125 mmol) in DMF (0.125 ml), a solution of HOAt (0.003125 mmol) Boc-AMH-OH [building 15 block 4] (0.003125 mmol) in DMF (1.25 ml) were added. The mixture was allowed to shake for 4 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

The resin was repeatedly (3 times) swelled in dichloromethane for 90 sec and filtered.

20

The compound was cleaved off the resin and deprotected by shaking for 10 min at -5 °C with a 50% solution of trifluoroacetic acid in dichloromethane (1.5 ml).

25 Ethanol (1.5 ml) was added and the mixture was filtered and concentrated in vacuo to give the desired compound.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

30

The RP-HPLC analysis was performed on a Waters HPLC system consisting of

Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5m C-18 Symmetry and Millennium QuickSet Control Ver. 2.15 using UV detection at 214 nm. A gradient of 5% to 90% acetonitrile/0.1 % trifluoroacetic acid/ water during
5 15 min at 1 ml/min.

The LC-MS analysis was performed on a PE Sciex API 100 LC/MS System using a Waters™ 3 mm x 150 mm 3.5m C-18 Symmetry column and positive ionspray with a flow rate at 20 ml/min.

10

15 EXAMPLES 159-253

The following 95 compounds were synthesized in parallel as individual entities analogously to example 158 on an Advanced ChemTech Model 384 HTS using
20 the following ChemFile to control the operation of the synthesizer (Advanced ChemTech Operator's Manual, version 1.2 July 1996, pp. 4-13):

ChemFile C:\ACT\CHEMFILE\2PETER.CHM Page 1

25

- 1 Flush Arm1 with DMF and NMP, Arm2 with DCM and DMF4
- 2 Empty RB1_1to96 for 3.000 minute(s)
- 3
- 30 4 Dispense System Fluid Dualarms_1+4* 1000 μ l to RB1_1to96[1-96]
- 5 Mix "RB1_1to96" for 2.00 minutes at 700 rpm(s)

- 6 Wait for 28.000 minute(s)
- 7 Empty RB1_1to96 for 3.000 minute(s)
- 8
- 9 REM Syntesestart her. Aminosyre 1
- 10 Dispense Sequence C:\ACT\displist\A1.DSP with 500 μ l to RB1_1to96 rack using DMF
- 11 Dispense Sequence C:\ACT\displist\A2.DSP with 500 μ l to RB1_1to96 rack using DMF
- 12 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 13 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- 14 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 15 Dispense System Fluid Dualarms_1+4* 500 μ l to RB1_1to96 [1-96]
- 16 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
- 17 Wait for 25.000 minute(s)
- 18 Repeat from step 16, 31 times
- 19 Pause
- 20 Empty RB1_1to96 for 3.000 minute(s)
- 21 Goto ChemFile WASH_DMF.CHM, line 1
- 22
- 23 REM Anden kobling 1ste AA
- 24 Dispense Sequence C:\ACT\displist\A1.DSP with 125 μ l to RB1_1to96 rack using DMF
- 25 Dispense Sequence C:\ACT\displist\A2.DSP with 125 μ l to RB1_1to96 rack using DMF
- 26 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 27 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- 28 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 29 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB1_1to96 [1-96]
- 30 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)

31 Wait for 25.000 minute(s)
32 Repeat from step 30, 9 times
33 Empty RB1_1to96 for 3.000 minute(s)
34 Pause
5 35 Goto ChemFile COUPLING.CHM, line 1
36 Pause
37
38 Goto ChemFile WASH_DMF.CHM, line 1
39 Goto ChemFile DEPROTEC.CHM, line 1
10 40 Goto ChemFile WASH_DMF.CHM, line 1
41
42 REM Her starter anden aminosyre-kobling
43 Dispense Sequence C:\ACT\displist\B1.DSP with 500µl to RB1_1to96 rack
using DMF
15 44 Dispense Sequence C:\ACT\displist\B2.DSP with 500µl to RB1_1to96 rack
using DMF
45 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
46 Transfer 500µl from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
47 Transfer 68µl from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using
20 DMF
48 Dispense System Fluid Dualarms_1+4* 500µl to RB1_1to96 [1-96]
49 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
50 Wait for 25.000 minute(s)
51 Repeat from step 49, 31 times
25 52
53 Empty RB1_1to96 for 3.000 minute(s)
54 Goto ChemFile WASH_DMF.CHM, line 1
55
56 REM Anden AA. Anden kobling
30 57 Dispense Sequence C:\ACT\displist\B1.DSP with 125µl to RB1_1to96 rack
using DMF

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- 58 Dispense Sequence C:\ACT\displist\B2.DSP with 125 μ l to RB1_1to96 rack using DMF
- 59 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 60 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- s 61 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 62 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB1_1to96 [1-96]
- 63 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
- 64 Wait for 25.000 minute(s)
- 10 65 Repeat from step 63, 9 times
- 66 Empty RB1 1to96 for 3.000 minute(s)
- 67 Goto ChemFile WASH_DMF.CHM, line 1
- 68 Goto ChemFile DEPROTEC.CHM, line 1
- 69 Goto ChemFile WASH_DMF.CHM, line 1
- 15 70
- 71 Pause
- 72
- 73 REM N-terminalkobling starter her
- 74 Dispense Sequence C:\ACT\displist\N1N2N3N4.DSP with 500 μ l to RB1_1to96 rack using DMF
- 75 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 76 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- 77 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 78 Dispense System Fluid Dualarms_1+4* 500 μ l to RB1_1to96 [1-96]
- 25 79 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
- 80 Wait for 25.000 minute(s)
- 81 Repeat from step 79, 20 times
- 82 Empty RB1 1to96 for 3.000 minute(s)
- 83 Goto ChemFile WASH_DMF.CHM, line 1
- 30 84
- 85 REM N-terminal. Anden kobling

86 Dispense Sequence C:\ACT\displist\N1N2N3N4.DSP with 125 μ l to RB1_1to96 rack using DMF

87 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)

88 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF

5 89 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF

90 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB1_1to96 [1-96]

91 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)

92 Wait for 25.000 minute(s)

93 Repeat from step 91, 9 times

10 94 Empty RB1_1to96 for 3.000 minute(s)

95 Goto ChemFile WASH_DMF.CHM, line 1

96 Goto ChemFile DEPROTEC.CHM, line 1

97 Goto ChemFile WASH_DMF.CHM, line 1

98

15

20 The building blocks were selected from the following groups:

[Building block 1]: N-Me-PAL, N-Phenethyl-PAL, N-(4-Pyridyl)ethyl-PAL, N-((S)-2-Hydroxypropyl)-PAL, N-(2,2-Dimethyl-3-hydroxypropyl)-PAL and N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL.

25

[Building block 2]: Fmoc-N-Me-D-Phe(4-F)-OH and Fmoc-N-Me-D-Phe(3,4-F,F)-OH.

[Building block 3]: Fmoc-N-Me-D-Nal-OH and Fmoc-N-Me-D-Phe(4-Phe)-OH.

30

[Building block 4]: Boc-AMH-OH, Boc-ACBB-OH, Boc-SPMA-OH and Boc-AEB-OH.

See Table 1

5

EXAMPLES 254-353

10 The following 100 compounds were synthesized in parallel as individual entities analogously to example 158 on an Advanced ChemTech Model 384 HTS using the following ChemFiles to control the operation of the synthesizer (Advanced ChemTech Operator's Manual, version 1.2 July 1996, pp. 4-13):

15

ChemFile C:\ACT\CHEMFILE\3PETER.CHM Page 1

20 1 Flush Arm1 with DMF and NMP, Arm2 with DCM and DMF4
2 Empty RB2_1to96 for 3.000 minute(s)
3
4 Dispense System Fluid Dualarms_1+4* 1000 μ l to RB2_1to96[1-96]
5 Mix "RB2_1to96" for 2.00 minutes at 700 rpm(s)
25 6 Wait for 28.000 minute(s)
7 Empty RB2_1to96 for 3.000 minute(s)
8
9 REM Syntesestart her. Aminosyre 1
10 Dispense Sequence C:\ACT\displist\A1.DSP with 500 μ l to RB2_1to96 rack
30 using DMF
11 Dispense Sequence C:\ACT\displist\A2.DSP with 500 μ l to RB2_1to96 rack
using DMF

12 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
13 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
14 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
5 15 Dispense System Fluid Dualarms_1+4* 500 μ l to RB2_1to96 [1-96]
16 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
17 Wait for 25.000 minute(s)
18 Repeat from step 16, 31 times
19 Pause
10 20 Empty RB2_1to96 for 3.000 minute(s)
21 Goto ChemFile WASH_DMF.CHM, line 1
22
23 REM Anden kobling 1ste AA
24 Dispense Sequence C:\ACT\displist\A1.DSP with 125 μ l to RB2_1to96 rack
15 using DMF
25 Dispense Sequence C:\ACT\displist\A2.DSP with 125 μ l to RB2_1to96 rack using DMF
26 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
27 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
20 28 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
29 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB2_1to96 [1-96]
30 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
31 Wait for 25.000 minute(s)
25 32 Repeat from step 30, 7 times
33 Empty RB2_1to96 for 3.000 minute(s)
34 Goto ChemFile WASH_DMF.CHM, line 1
35 Pause
36
30 37 Goto ChemFile DEPROTEC.CHM, line 1
38 Goto ChemFile WASH_DMF.CHM, line 1

39

40 REM Her starter anden aminosyre-kobling

41 Dispense Sequence C:\ACT\displist\B1.DSP with 500 μ l to RB2_1to96 rack using DMF

5 42 Dispense Sequence C:\ACT\displist\B2.DSP with 500 μ l to RB2_1to96 rack using DMF

43 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)

44 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF

45 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using

10 DMF

46 Dispense System Fluid Dualarms_1+4* 500 μ l to RB2_1to96 [1-96]

47 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)

48 Wait for 25.000 minute(s)

49 Repeat from step 47, 31 times

15 50

51 Empty RB2_1to96 for 3.000 minute(s)

52 Goto ChemFile WASH_DMF.CHM, line 1

53

54 REM Anden AA. Anden kobling

20 55 Dispense Sequence C:\ACT\displist\B1.DSP with 125 μ l to RB2_1to96 rack using DMF

56 Dispense Sequence C:\ACT\displist\B2.DSP with 125 μ l to RB2_1to96 rack using DMF

57 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)

25 58 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF

59 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF

60 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB2_1to96 [1-96]

61 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)

30 62 Wait for 25.000 minute(s)

63 Repeat from step 61, 7 times

64 Empty RB2_1to96 for 3.000 minute(s)
65 Goto ChemFile WASH_DMF.CHM, line 1
66 Pause
67
5 68 Goto ChemFile DEPROTEC.CHM, line 1
69 Goto ChemFile WASH_DMF.CHM, line 1
70
71 Pause
72
10 73 REM N-terminalkobling starter her
74 Dispense Sequence C:\ACT\displist\N_56789.DSP with 500µl to RB2_1to96
rack using DMF
75 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
76 Transfer 500µl from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
15 77 Transfer 68µl from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
78 Dispense System Fluid Dualarms_1+4* 500µl to RB2_1to96 [1-96]
79 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
80 Wait for 25.000 minute(s)
81 Repeat from step 79, 20 times
20 82 Empty RB2_1to96 for 3.000 minute(s)
83 Goto ChemFile WASH_DMF.CHM, line 1
84
85 REM N-terminal. Anden kobling
86 Dispense Sequence C:\ACT\displist\N_56789.DSP with 125µl to RB2_1to96
25 rack using DMF
87 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
88 Transfer 125µl from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
89 Transfer 20µl from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
90 Dispense System Fluid Dualarms_1+4* 1250µl to RB2_1to96 [1-96]
30 91 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
92 Wait for 25.000 minute(s)

93 Repeat from step 91, 7 times
94 Empty RB2 1to96 for 3.000 minute(s)
95 Goto ChemFile WASH_DMF.CHM, line 1
96 Goto ChemFile WASH_DCM.CHM, line 1
s 97

The building blocks were selected from the following groups:

10 [Building block 1]: N-Phenethyl-PAL, N-(4-Pyridyl)ethyl-PAL, N-((S)- 2-Hydroxypropyl)-PAL, N-(2,2-Dimethyl-3-hydroxypropyl)-PAL and N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL.

15 [Building block 2]: Fmoc-N-Me-D-Phe(4-F)-OH and Fmoc-N-Me-D-Phe(3,4-F,F)-OH.
[Building block 3]: Fmoc-N-Me-D-Nal-OH and Fmoc-N-Me-D-Phe(4-Phe)-OH.

20 [Building block 4]: Boc-AMB-OH, Boc-ADH-OH, Boc-MAMH-OH, Boc-RPMA-OH and Boc-AEHA-OH.

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See Table 2

EXAMPLES 354-533

The following 180 compounds were synthesized in parallel as individual entities analogously to example 158 on an Advanced ChemTech Model 384 HTS using
5 the following ChemFiles to control the operation of the synthesizer (Advanced ChemTech Operator's Manual, version 1.2 July 1996, pp. 4-13):

ChemFile C:\ACT\CHEMFILE\4PETER.CHM Page 1

10

- 1 Flush Arm1 with DMF and THF, Arm2 with DCM and DMF4
- 2 Empty RB3_1to96 for 3.000 minute(s)
- 3 Empty RB4_1to96 for 3.000 minute(s)

15 4

- 5 Dispense System Fluid Dualarms_1+4* 1500 μ l to RB3_1to96[1-96]
- 6 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 7 Dispense System Fluid Dualarms_1+4* 1500 μ l to RB4_1to96[1-96]
- 8 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

20 9 Empty RB3_1to96 for 3.000 minute(s)

10 Empty RB4_1to96 for 3.000 minute(s)

11

12 REM !! SYNTESESTART HER !!

13

25 14 REM Aminosyre 1

15 Dispense Sequence C:\ACT\displist\A3_3.DSP with 500 μ l to RB3_1to96 rack using DMF

16 Dispense Sequence C:\ACT\displist\A4_3.DSP with 500 μ l to RB3_1to96 rack using DFM

30 17 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

18 Dispense Sequence C:\ACT\displist\A1A2_4.DSP with 500 μ l to RB4_1to96 rack using DMF

19 Dispense Sequence C:\ACT\displist\A3_4.DSP with 500 μ l to RB4_1to96 rack using DMF

20 Dispense Sequence C:\ACT\displist\A4_4.DSP with 500 μ l to RB4_1to96 rack using DMF

5 21 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

22 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF

23 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

24 Transfer 500 μ l from REAGENT_3 [1] (HATU) to RB4_1to96 [1-96] using DMF4

10 25 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

26 Dispense System Fluid Dualarms_1+4* 500 μ l to RB3_1to96 [1-96]

27 Dispense System Fluid Dualarms_1+4* 500 μ l to RB4_1to96 [1-96]

28 Transfer 68 μ l from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF

15 29 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)

30 Transfer 68 μ l from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF4

31 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)

32 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)

20 33 Wait for 25.000 minute(s)

34 Repeat from step 31, 31 times

35 Empty RB3_1to96 for 3.000 minute(s)

36 Empty RB4_1to96 for 3.000 minute(s)

37 Goto ChemFile WASH_DMF.CHM, line 1

25 38

39 REM Anden kobling 1ste AA

40 Dispense Sequence C:\ACT\displist\A3_3.DSP with 125 μ l to RB3_1to96 rack using DMF

41 Dispense Sequence C:\ACT\displist\A4_3.DSP with 125 μ l to RB3_1to96 rack

30 using DMF

42 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

43 Dispense Sequence C:\ACT\displist\A1A2_4.DSP with 125 μ l to RB4_1to96 rack using DMF

44 Dispense Sequence C:\ACT\displist\A3_4.DSP with 125 μ l to RB4_1to96 rack using DMF

5 45 Dispense Sequence C:\ACT\displist\A4_4.DSP with 125 μ l to RB4_1to96 rack using DMF

46 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

47 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF

48 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

10 49 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4

50 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

51 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB3_1to96 [1-96]

52 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB4_1to96 [1-96]

15 53 Transfer 20 μ l from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF

54 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)

55 Transfer 20 μ l from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF4

20 56 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)

57 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)

58 Wait for 25.000 minute(s)

59 Repeat from step 56, 7 times

60 Empty RB3_1to96 for 3.000 minute(s)

25 61 Empty RB4_1to96 for 3.000 minute(s)

62

63 Goto ChemFile WASH_DMF.CHM, line 1

64 Goto ChemFile DEPROTEC.CHM, line 1

65 Goto ChemFile WASH_DMF.CHM, line 1

30 66

67 Pause

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69 REM Start anden AA-kobling

70 Dispense Sequence C:\ACT\displist\B1_3.DSP with 500 μ l to RB3_1to96 rack using DMF

5 71 Dispense Sequence C:\ACT\displist\B2_3.DSP with 500 μ l to RB3_1to96 rack using DMF

72 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

73 Dispense Sequence C:\ACT\displist\B1_4.DSP with 500 μ l to RB4_1to96 rack using DMF

10 74 Dispense Sequence C:\ACT\displist\B2_4.DSP with 500 μ l to RB4_1to96 rack using DMF

75 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

76 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF

77 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

15 78 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4

79 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)

80 Dispense System Fluid Dualarms_1+4* 500 μ l to RB3_1to96 [1-96]

81 Dispense System Fluid Dualarms_1+4* 500 μ l to RB4_1to96 [1-96]

20 82 Transfer 68 μ l from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF

83 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)

84 Transfer 68 μ l from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF4

25 85 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)

86 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)

87 Wait for 25.000 minute(s)

88 Repeat from step 85, 31 times

89 Empty RB3_1to96 for 3.000 minute(s)

30 90 Empty RB4_1to96 for 3.000 minute(s)

91 Goto ChemFile WASH_DMF.CHM, line 1

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- 92
- 93 REM Anden kobling anden AA
- 94 Dispense Sequence C:\ACT\displist\B1_3.DSP with 125µl to RB3_1to96 rack using DMF
- 95 Dispense Sequence C:\ACT\displist\B2_3.DSP with 125µl to RB3_1to96 rack using DMF
- 96 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 97 Dispense Sequence C:\ACT\displist\B1_4.DSP with 125µl to RB4_1to96 rack using DMF
- 98 Dispense Sequence C:\ACT\displist\B2_4.DSP with 125µl to RB4_1to96 rack using DMF
- 99 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 100 Transfer 125µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
- 101 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 102 Transfer 125µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF
- 103 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 104 Dispense System Fluid Dualarms_1+4* 1250µl to RB3_1to96 [1-96]
- 105 Dispense System Fluid Dualarms_1+4* 1250µl to RB4_1to96 [1-96]
- 106 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF
- 107 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
- 108 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF
- 109 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
- 110 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
- 111 Wait for 25.000 minute(s)
- 112 Repeat from step 109, 7 times
- 113 Empty RB3_1to96 for 3.000 minute(s)
- 114 Empty RB4_1to96 for 3.000 minute(s)
- 115

116 Goto ChemFile WASH_DMF.CHM, line 1
117 Goto ChemFile DEPROTEC.CHM, line 1
118 Goto ChemFile WASH_DMF.CHM, line 1
119

5 120 Pause
121
122 REM N-terminal coupling start
123 Dispense Sequence C:\ACT\displist\N_3.DSP with 500µl to RB3_1to96 rack using DMF

10 124 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
125 Dispense Sequence C:\ACT\displist\N_4.DSP with 500µl to RB4_1to96 rack using DMF

126 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
127 Transfer 500µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF

15 128 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
129 Transfer 500µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4

130 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
131 Dispense System Fluid Dualarms_1+4* 500µl to RB3_1to96 [1-96]

20 132 Dispense System Fluid Dualarms_1+4* 500µl to RB4_1to96 [1-96]
133 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF

134 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
135 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using

25 DMF4
136 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
137 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
138 Wait for 25.000 minute(s)
139 Repeat from step 136, 31 times

30 140 Empty RB3_1to96 for 3.000 minute(s)
141 Empty RB4_1to96 for 3.000 minute(s)

142 Goto ChemFile WASH_DMF.CHM, line 1
143
144 REM
145 Dispense Sequence C:\ACT\displist\N_3.DSP with 125 μ l to RB3_1to96 rack
5 using DMF
146 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
147 Dispense Sequence C:\ACT\displist\N_4.DSP with 125 μ l to RB4_1to96 rack
using DMF
148 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
10 149 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
150 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
151 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using
DMF4
152 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
15 153 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB3_1to96 [1-96]
154 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB4_1to96 [1-96]
155 Transfer 20 μ l from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using
DMF
156 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
20 157 Transfer 20 μ l from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using
DMF4
158 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
159 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
160 Wait for 25.000 minute(s)
25 161 Repeat from step 158, 7 times
162 Empty RB3_1to96 for 3.000 minute(s)
163 Empty RB4_1to96 for 3.000 minute(s)
164 Goto ChemFile WASH_DMF.CHM, line 1
165

The building blocks were selected from the following groups:

[Building block 1]: N-Phenethyl-PAL, N-(4-Pyridyl)ethyl-PAL, N-((S)- 2-Hydroxypropyl)-PAL, N-(2,2-Dimethyl-3-hydroxypropyl)-PAL and N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL.

[Building block 2]: Fmoc-N-Me-D-Phe-OH and Fmoc-N-Me-D-ThiAla-OH.

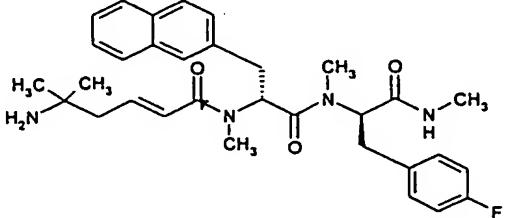
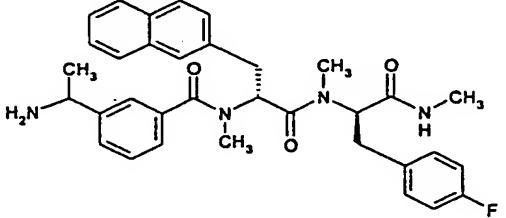
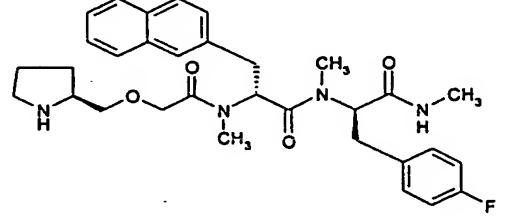
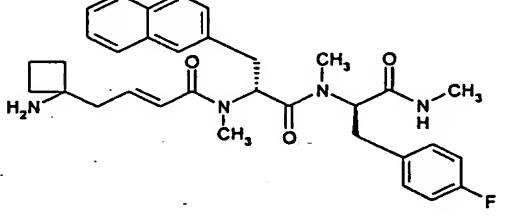
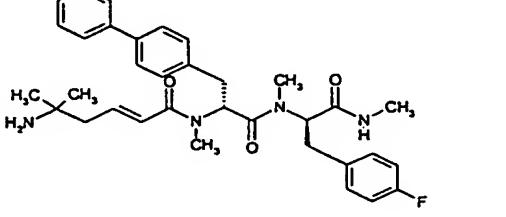
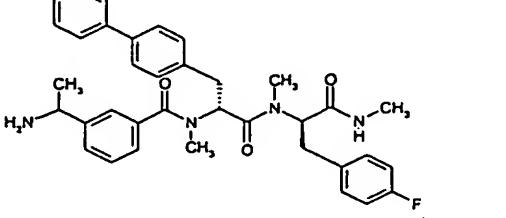
10 [Building block 3]: Fmoc-N-Me-D-Nal-OH and Fmoc-N-Me-D-Phe(4-Phe)-OH.

[Building block 4]: Boc-AMH-OH, Boc-ACBMA-OH, Boc-RPMA-OH, Boc-AEB-
15 OH, Boc-AMB-OH, Boc-ADH-OH, Boc-MAMH-OH, Boc-RPMA-OH and Boc-AEHA-OH.

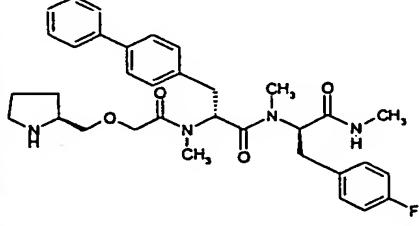
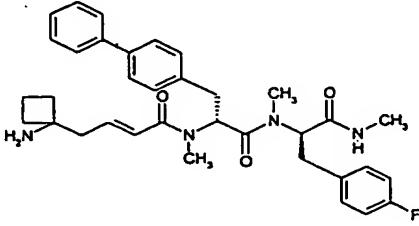
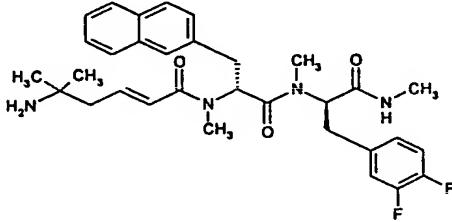
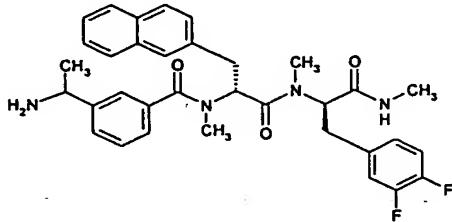
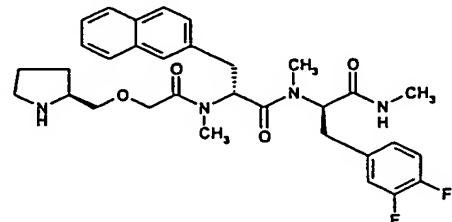
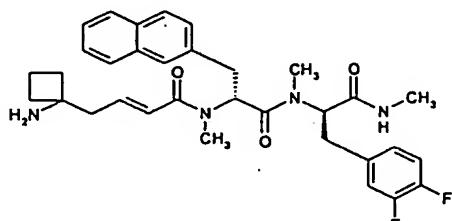
See Table 3

Table 1

10067895 - DRUGS

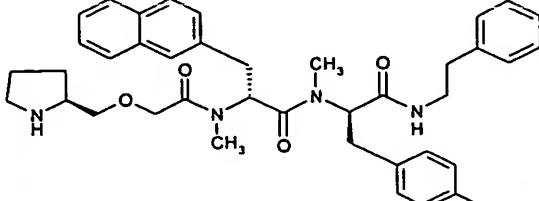
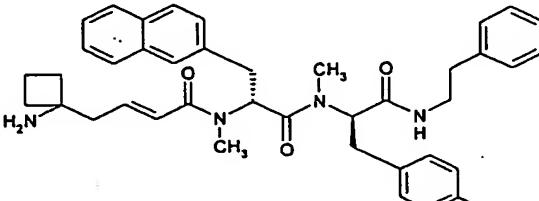
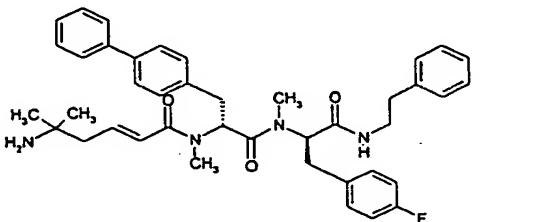
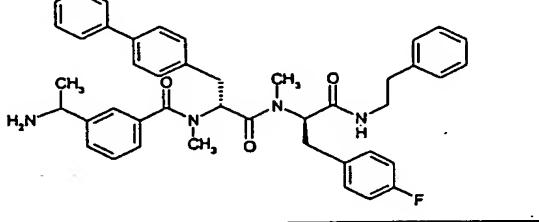
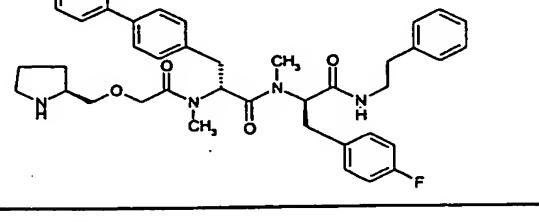
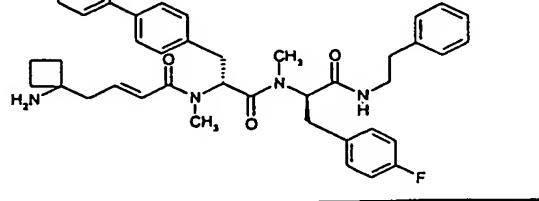
Example	Structure	MW	HPLC	LCMS
158		546,7	9,91	546,8
159		568,7	9,68	569,0
160		562,7	9,38	563,0
161		558,7	9,63	559,0
162		572,7	10,11	573,0
163		594,7		

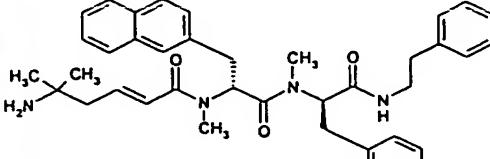
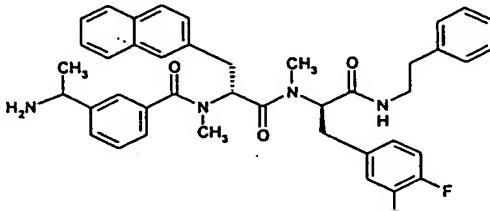
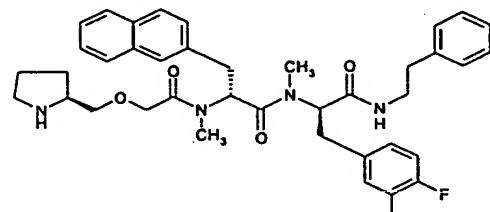
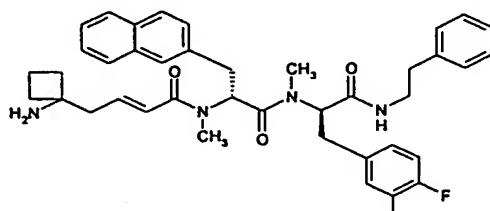
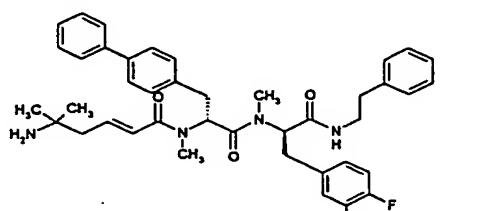
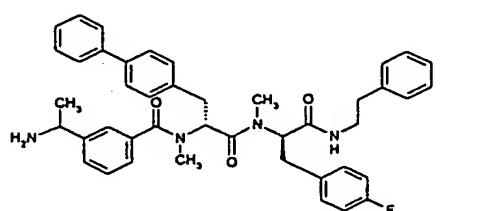
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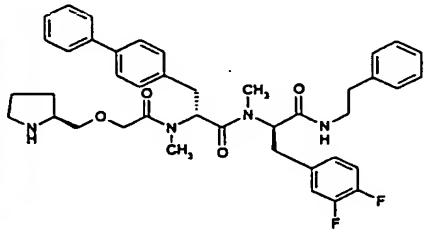
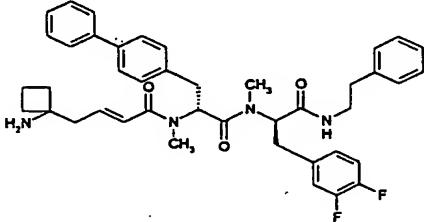
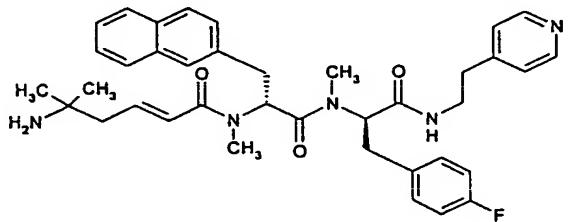
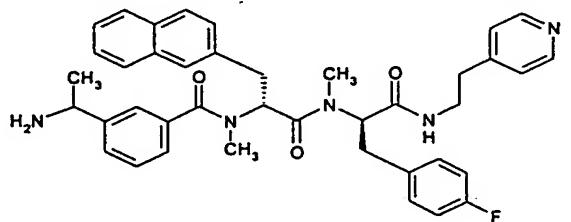
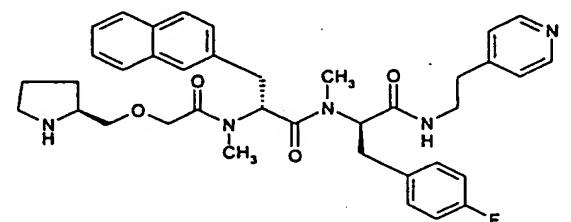
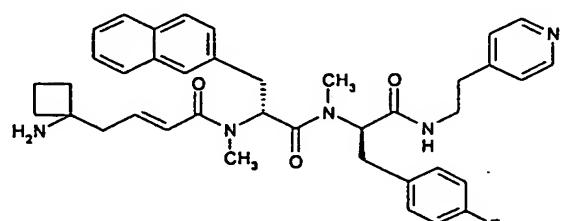
164		588,7	10,02	589,2
165		584,7		
166		564,7	9,68	565,0
167		586,7	9,83	587,2
168		580,7	9,61	581,0
169		576,7		576,8

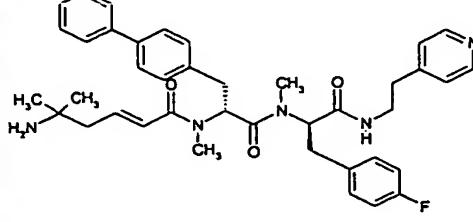
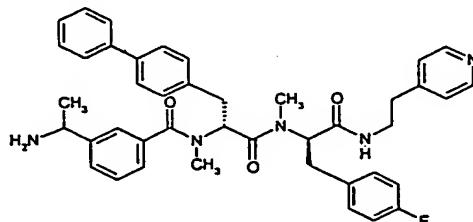
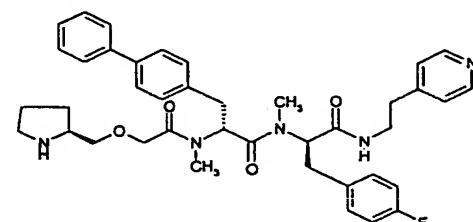
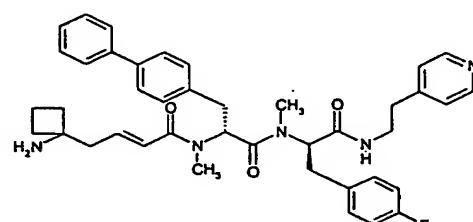
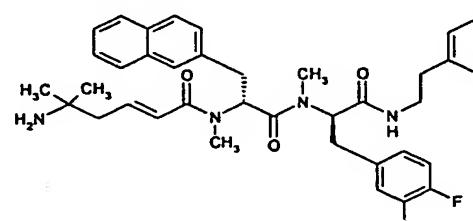
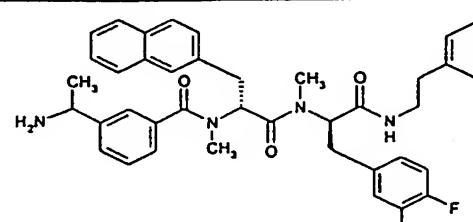
170		590,7		
171		612,7	10,49	613,2
172		606,7	10,26	607,0
173		602,7	10,50	603,0
174		636,8	10,73	637,2
175		658,8	10,97	659,2

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176		652,8	11,07	653,2
177		648,8		
178		662,9	11,56	663,2
179		684,9	11,81	685,0
180		678,9	11,60	679,0
181		674,9	11,95	675,2

182		654,8	11,28	655,0
183		676,8	11,40	677,2
184		670,8	11,27	672,2
185		666,8	11,44	667,2
186		680,8	11,80	681,0
187		702,9	12,10	702,8

188		696,8	11,97	697,0
189		692,9		
190		637,8	8,06	638,2
191		659,8	8,27	660,0
192		653,8	8,05	654,2
193		649,8	8,33	650,2

194		663,8	8,44	664,2
195		685,8	8,84	686,0
196		679,8	8,61	680,0
197		675,9		
198		655,8	8,37	656,0
199		677,8	8,45	678,0

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200		671,8	8,26	672,2
201		667,8	8,51	668,0
202		681,8	8,52	682,0
203		703,8	8,63	704,0
204		697,8	8,79	689,2
205		693,8	8,99	

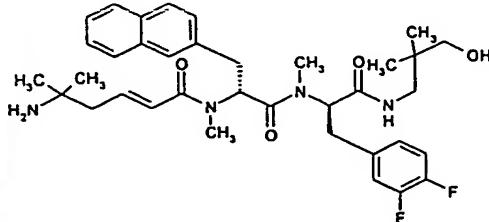
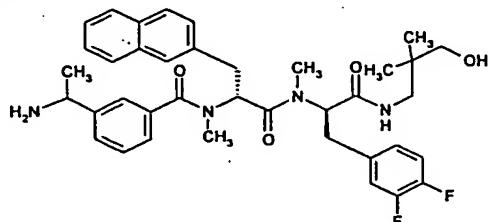
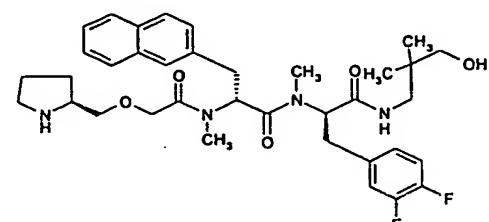
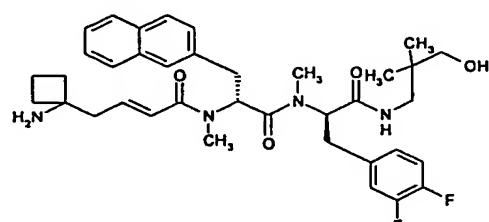
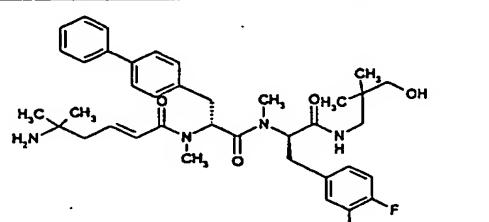
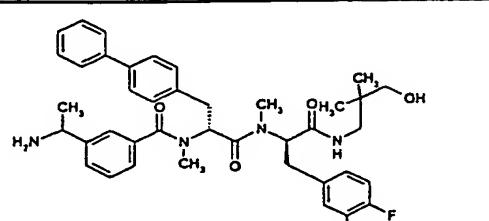
206		643,9	7,95	644,2
207		665,9	8,08	666,2
208		659,9	8,15	660,0
209		655,9	8,35	656,2
210		669,9	8,77	670,2
211		691,9	8,93	692,2

212		685,9	8,70	686,0
213		681,9		
214		661,8	7,88	662,2
215		683,8	8,53	684,0
216		677,8	8,36	678,0
217		673,9		

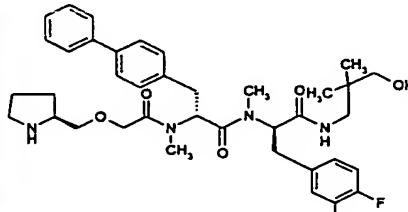
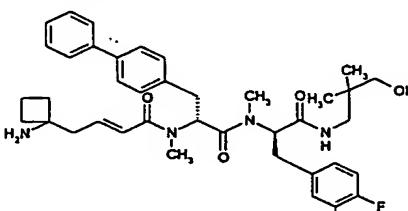
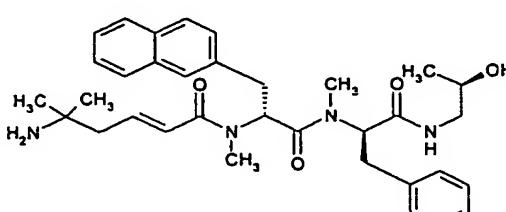
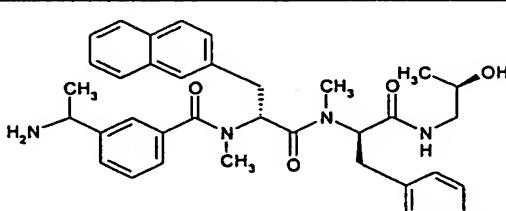
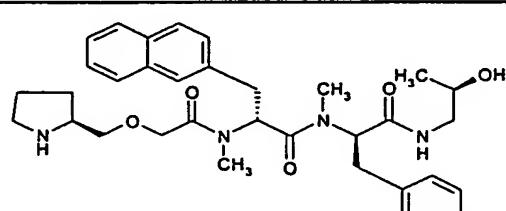
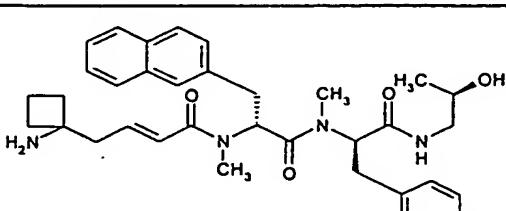
218		687,9		
219		709,9	9,11	710,0
220		703,9	8,91	705,0
221		699,9		
222		618,8	9,18	619,0
223		640,8		

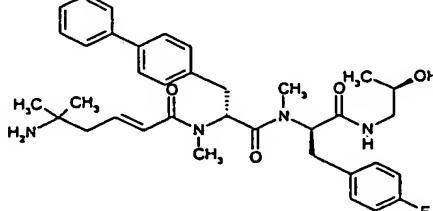
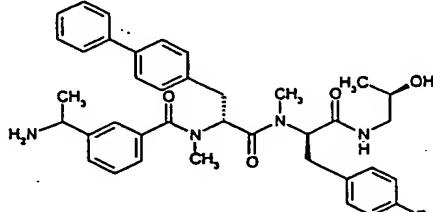
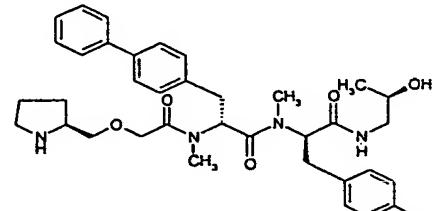
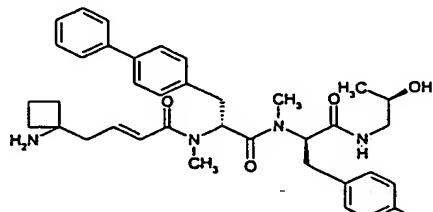
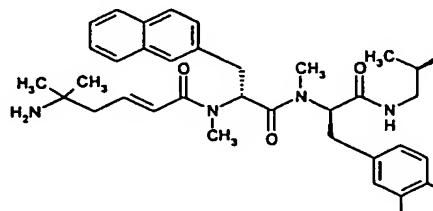
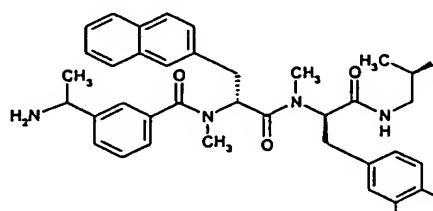
10067695 - DECODE

224		634,8	9,42	635,2
225		630,8	9,98	629,8
226		644,8		
227		666,8	10,78	667,4
228		660,8		
229		656,8		

230		636,8		
231		658,8	9,90	658,0
232		652,8	9,66	653,0
233		648,8		
234		662,8	10,34	663,0
235		684,8		

H O O C S E G E D E D O R

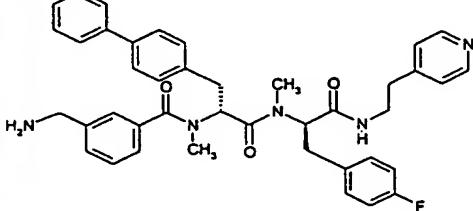
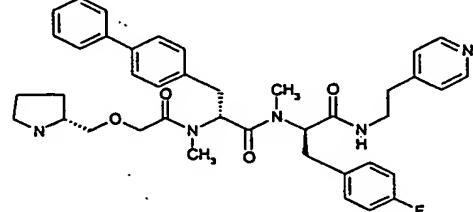
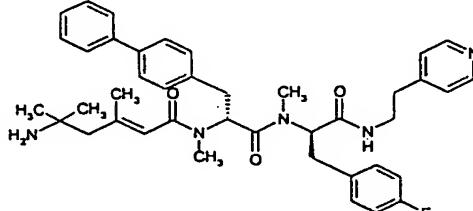
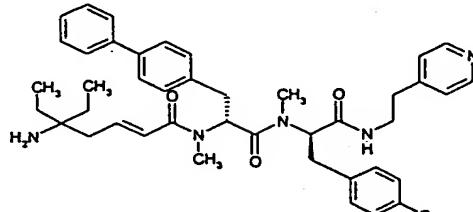
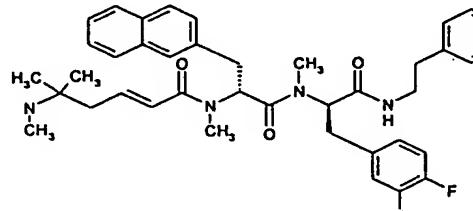
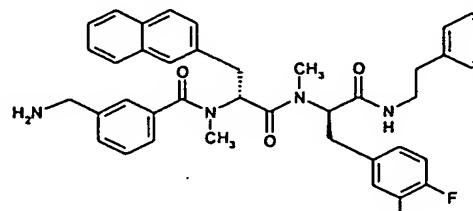
236		678,8	10,01	679,2
237		674,8		
238		590,7	8,48	591,0
239		612,8	9,52	613,0
240		606,7	9,28	607,0
241		602,8	9,59	603,0

242		616,8	9,05	617,2
243		638,8	8,97	639,0
244		632,8		633,0
245		628,8		629,0
246		608,7	9,12	608,8
247		630,7	9,72	631,0

248		624,7	9,51	625,0
249		620,7	9,26	621,0
250		634,8		
251		656,8	9,50	656,8
252		650,8	9,50	651,0
253		646,8	9,48	

Table 2

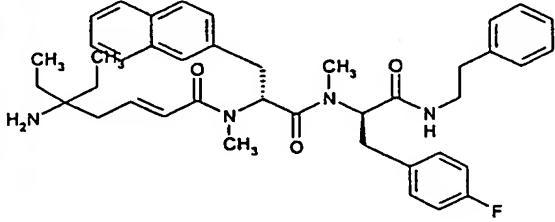
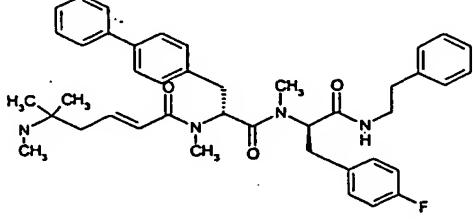
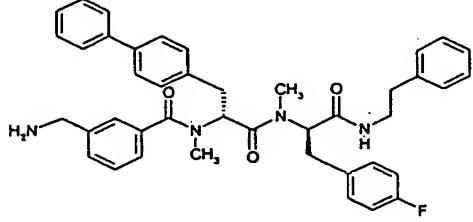
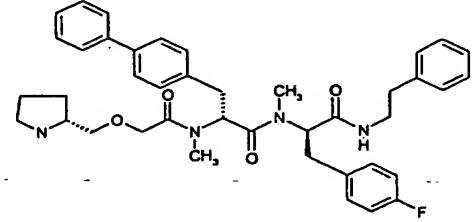
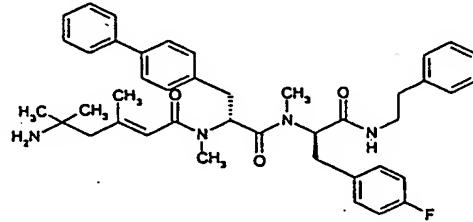
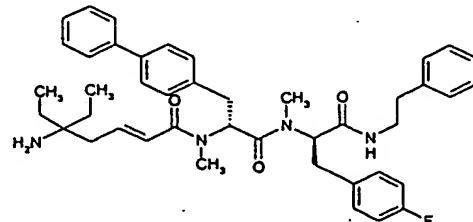
Example	Structure	MW	HPLC	LC-MS
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255		645,78		
256		653,80		
257		651,83		
258		665,86		
259		677,87		

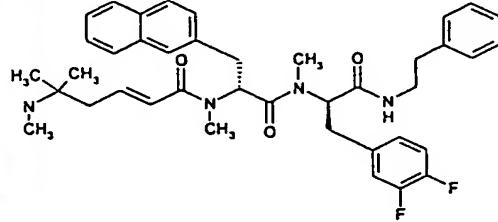
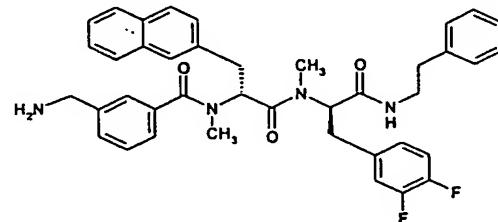
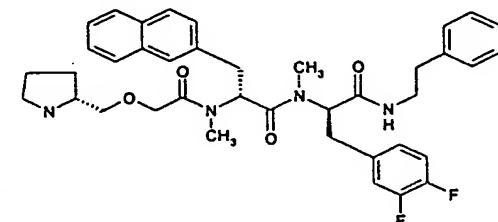
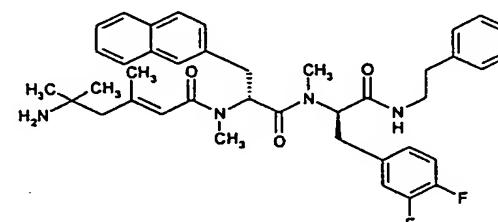
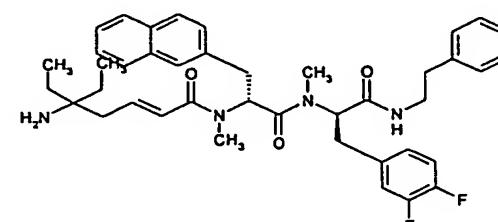
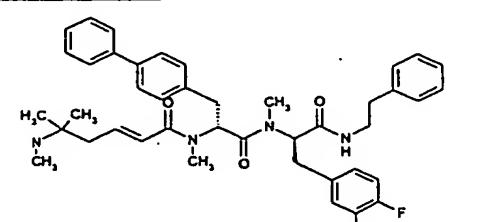
260		671,82		
261		679,84		
262		677,87		
263		691,90		
264		669,82		
265		663,77		

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266		671,79		
267		669,82		
268		683,85		
269		695,86		
270		689,81		
271		697,83		

272		695,86		
273		709,89		
274		650,84		
275		644,80		
276		652,82		
277		650,84		

278		664,87		
279		676,88		
280		670,83		
281		678,85		
282		676,88		
283		690,91		

284		668,83		
285		662,79		
286		670,81		
287		668,83		
288		682,86		
289		694,87		

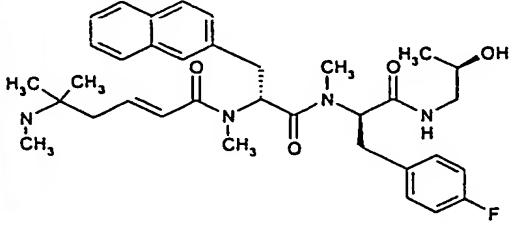
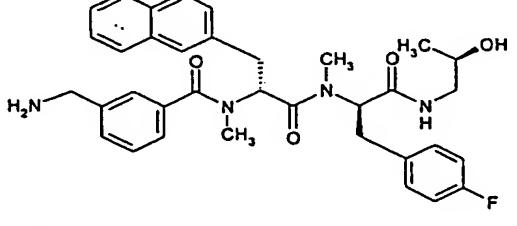
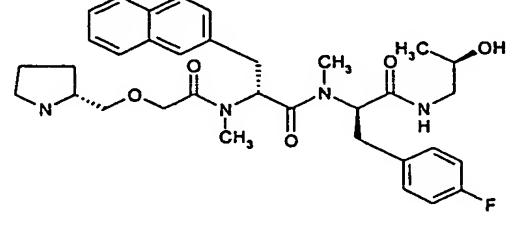
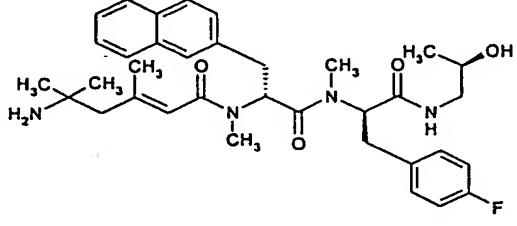
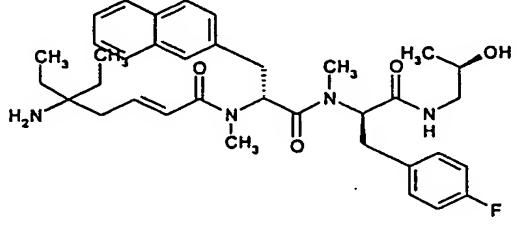
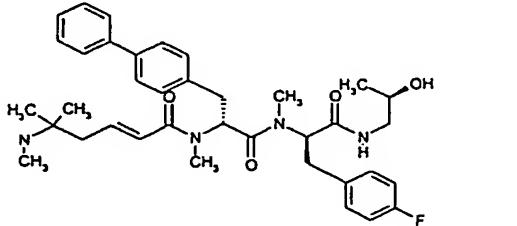
290		688,82		
291		696,84		
292		694,87		
293		708,90		
294		657,88		
295		651,83		

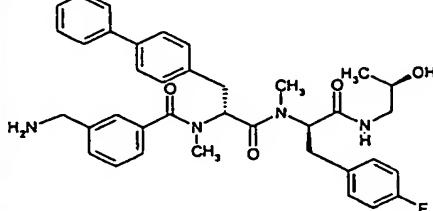
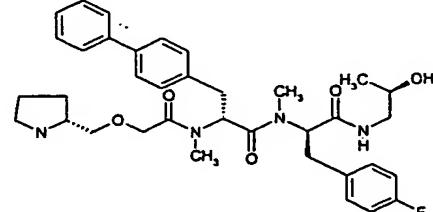
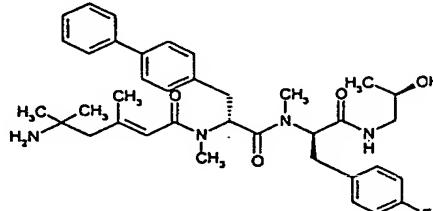
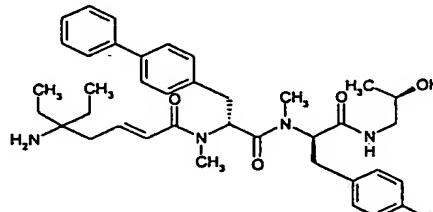
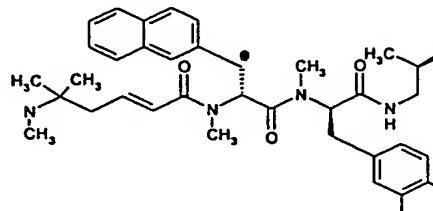
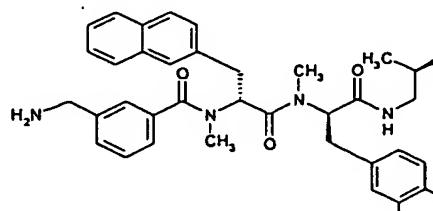
296		659,85		
297		657,88		
298		671,91		
299		683,92		
300		677,87		
301		685,89		

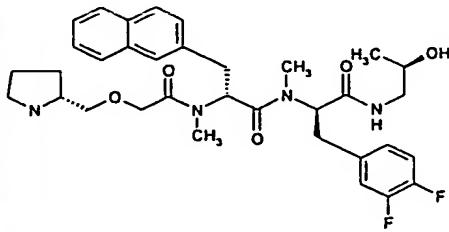
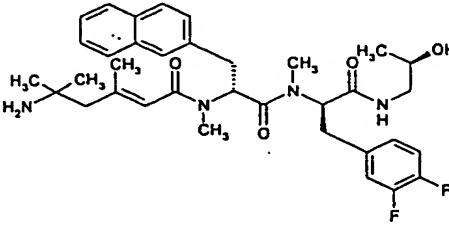
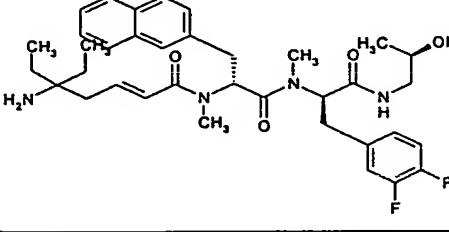
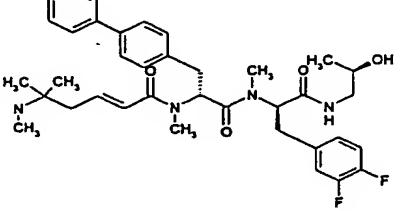
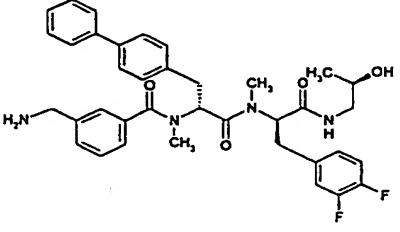
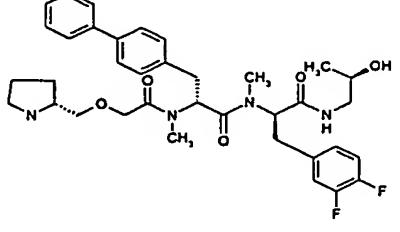
THERAPEUTIC DRUGS

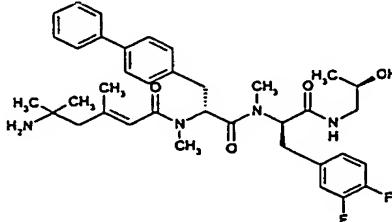
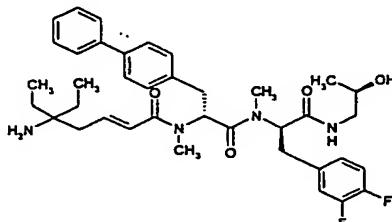
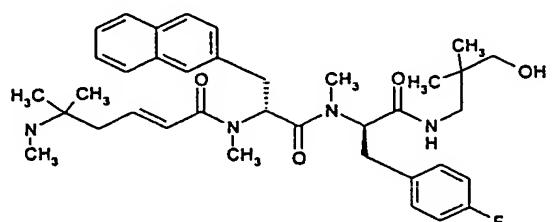
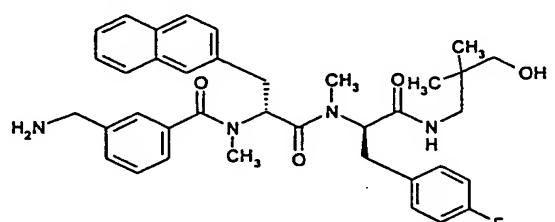
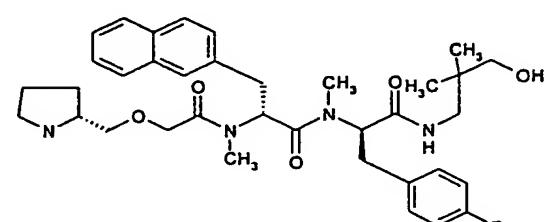
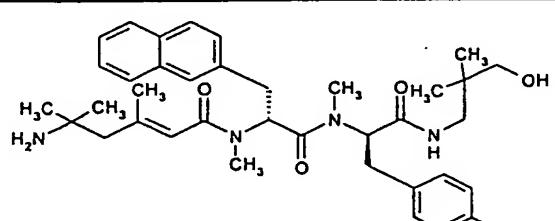
302		683,92		
303		697,94		
304		675,87		
305		669,82		
306		677,84		
307		675,87		

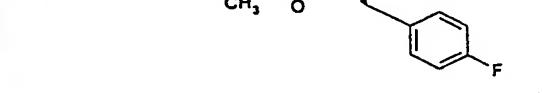
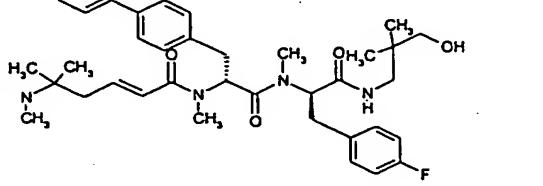
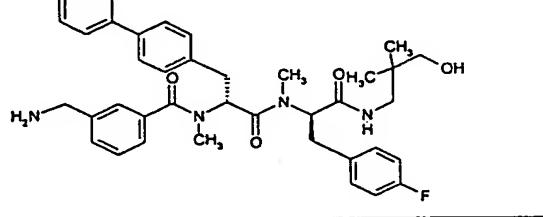
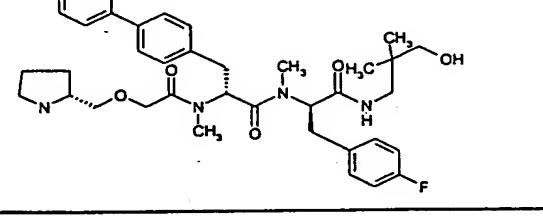
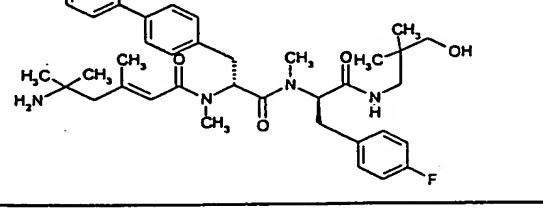
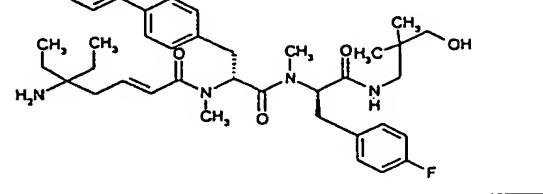
308		689,90		
309		701,91		
310		695,86		
311		703,88		
312		701,91		
313		715,94		

314		604,77		
315		598,72		
316		606,74		
317		604,77		
318		618,80		
319		630,81		

320		624,76		
321		632,78		
322		630,81		
323		644,84		
324		622,76		
325		616,71		

326		624,73		
327		622,76		
328		636,79		
329		648,80		
330		642,75		
331		650,77		

332		648,80		
333		662,83		
334		632,83		
335		626,78		
336		634,80		
337		632,83		

338		646,85	
339		658,86	
340		652,82	
341		660,84	
342		658,86	
343		672,89	

344		650,82		
345		644,77		
346		652,79		
347		650,82		
348		664,84		
349		676,85		

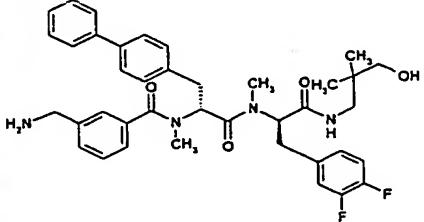
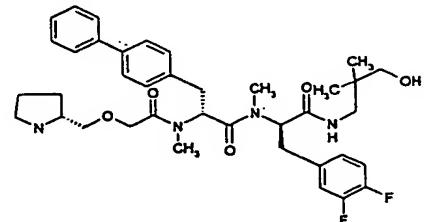
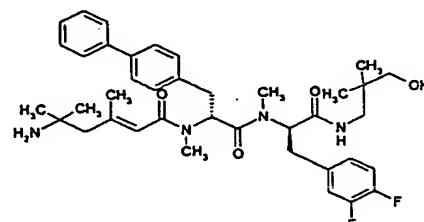
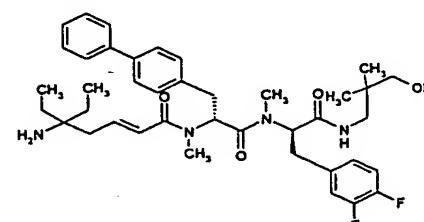
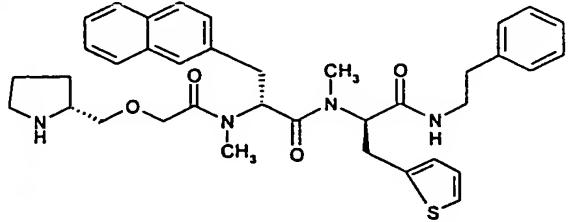
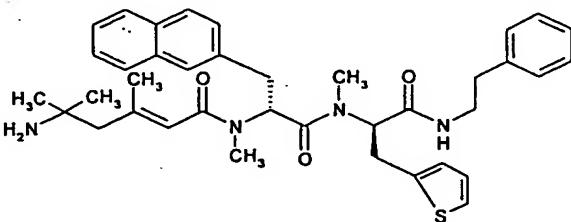
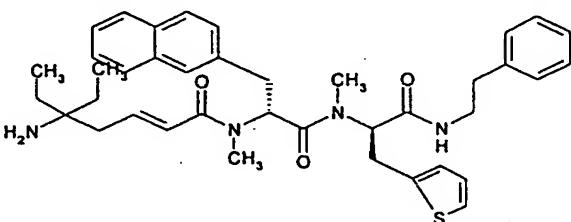
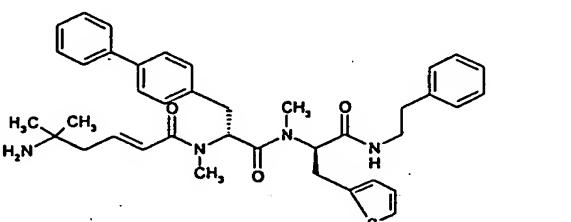
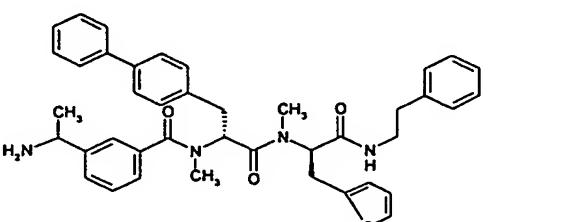
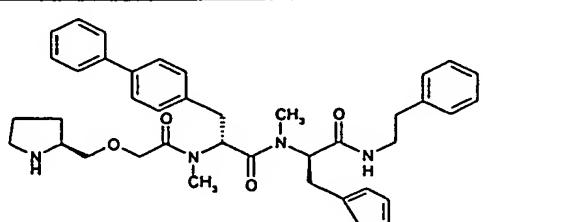
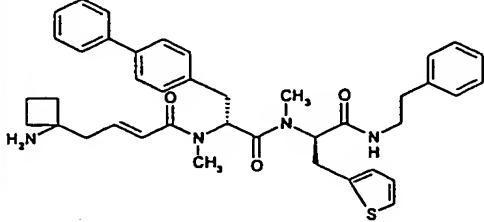
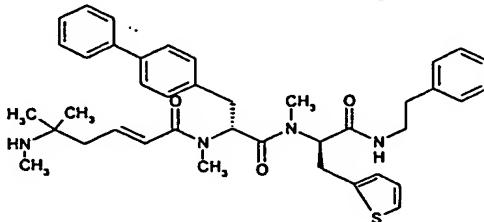
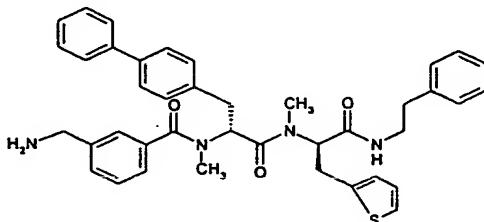
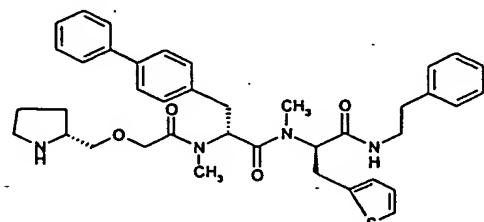
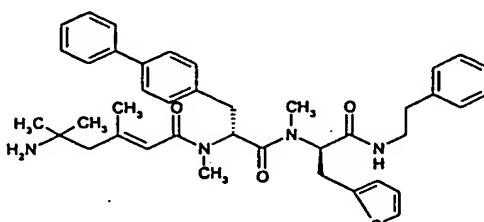
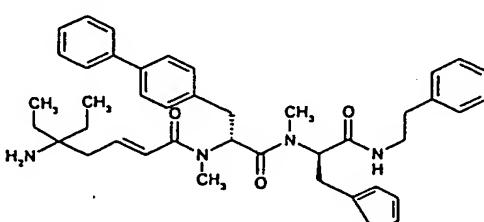
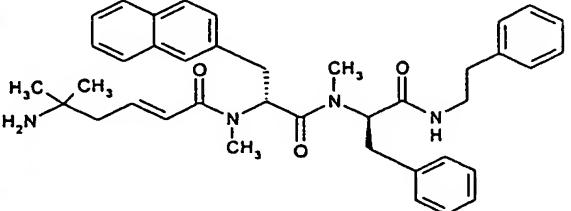
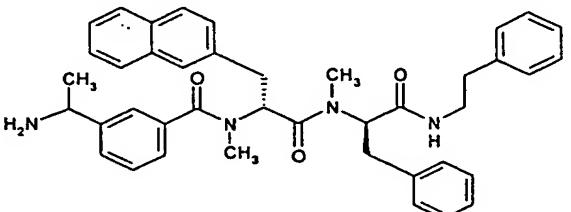
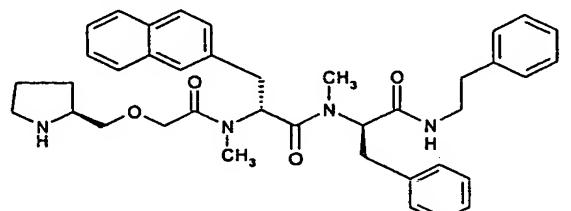
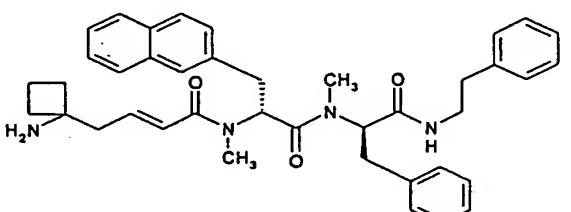
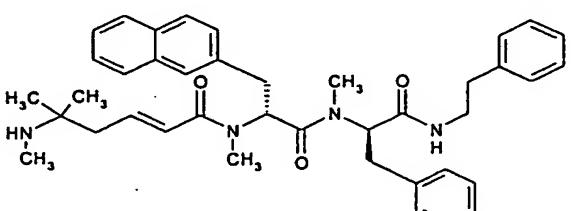
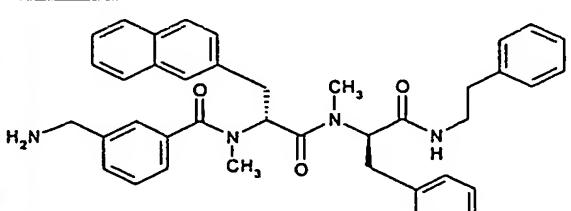
350		670,81		
351		678,83		
352		676,85		
353		690,88		

Table 3

Example	Structure	MW	HPLC	LC-MS
354		624,9		
355		646,9		
356		640,9		
357		636,9		
358		638,9		
359		632,8		

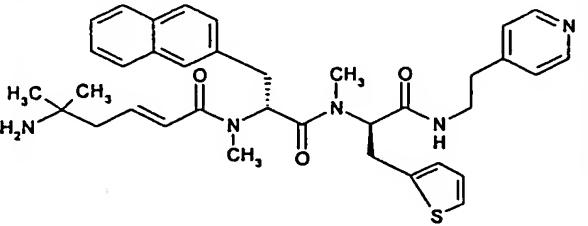
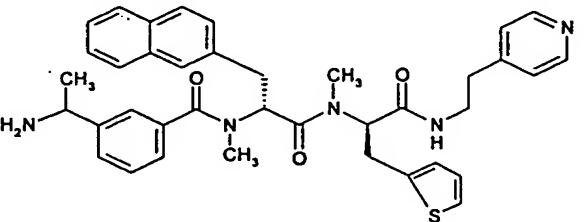
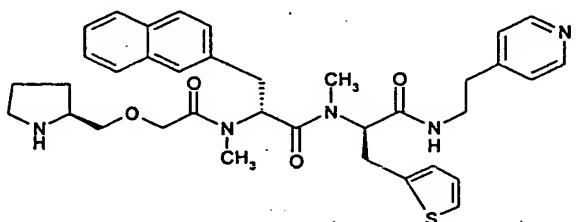
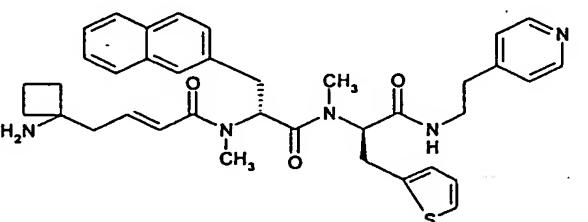
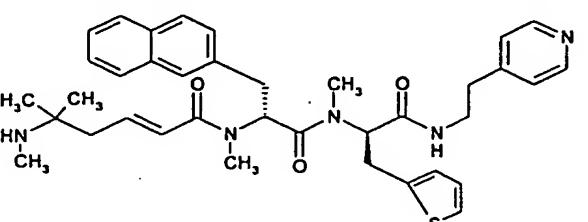
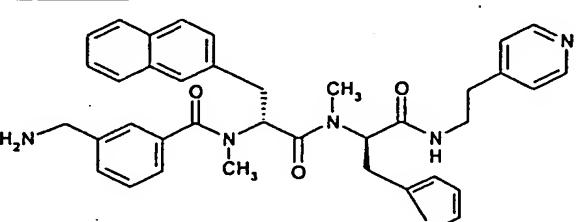
360		640,9		
361		638,9		
362		652,9		
363		650,9		
364		672,9		
365		666,9		

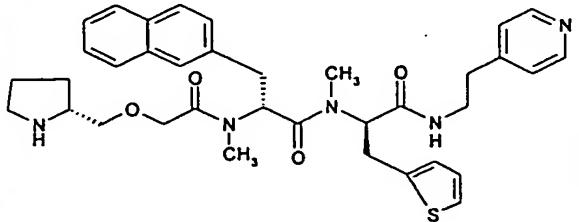
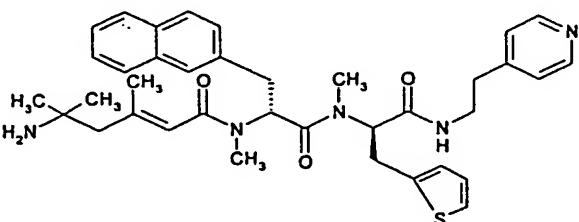
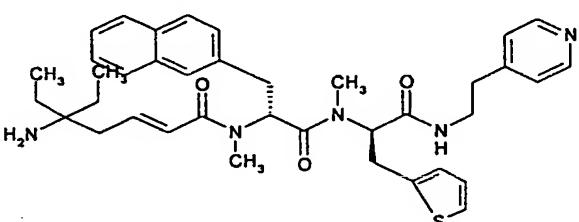
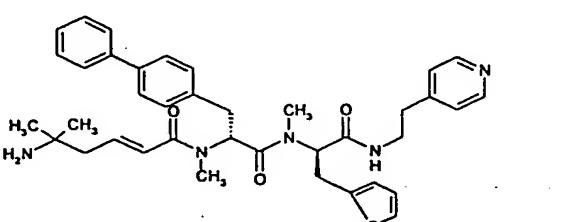
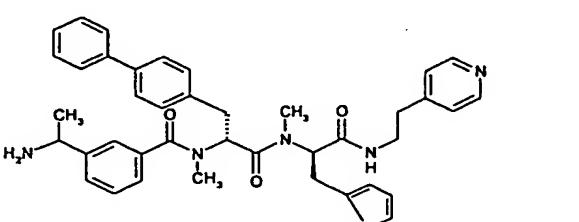
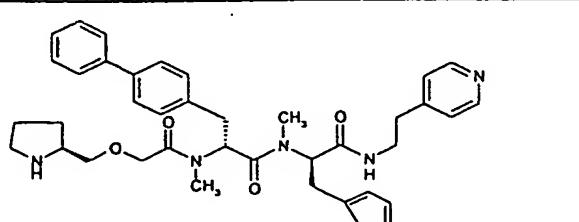
366		662,9		
367		664,9		
368		658,9		
369		666,9		
370		664,9		
371		678,9		

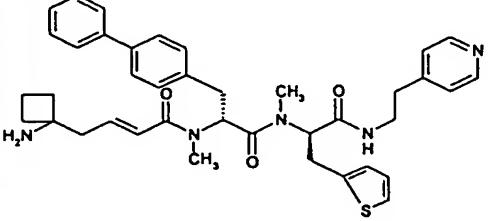
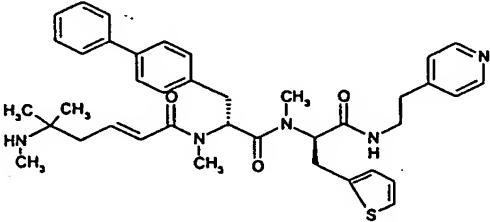
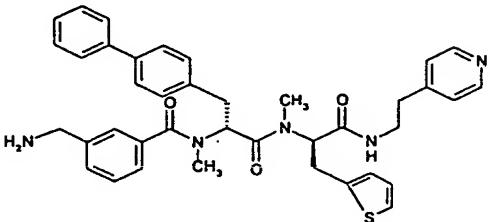
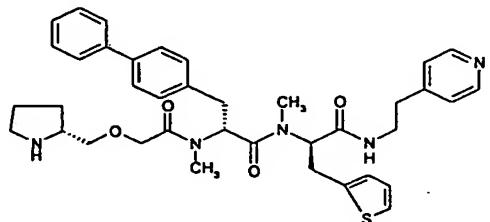
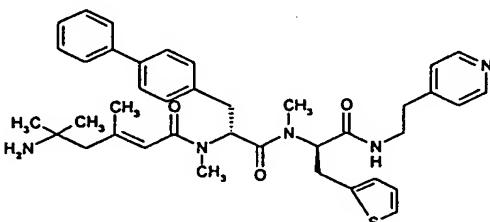
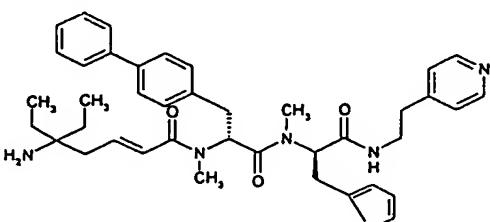
372		618,8		
373		640,8		
374		634,8		
375		630,8		
376		632,9		
377		626,8		

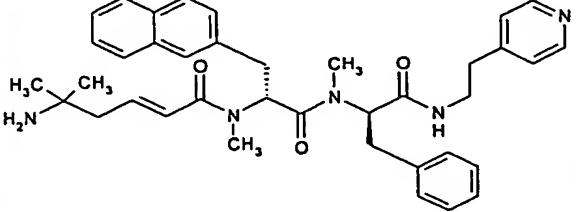
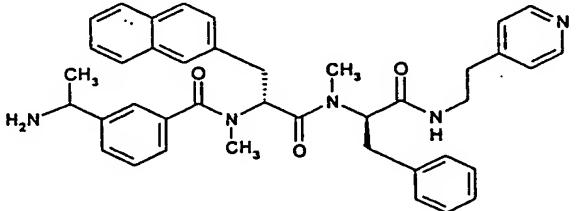
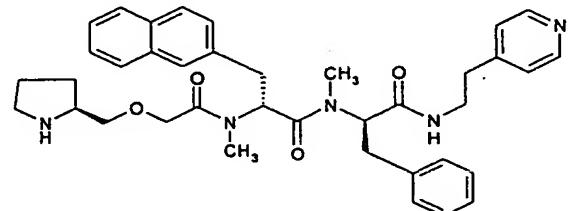
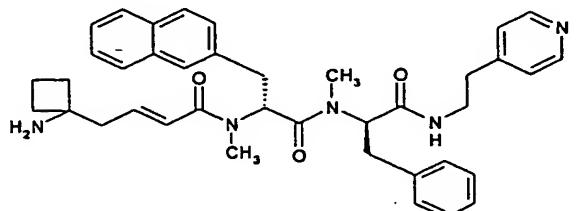
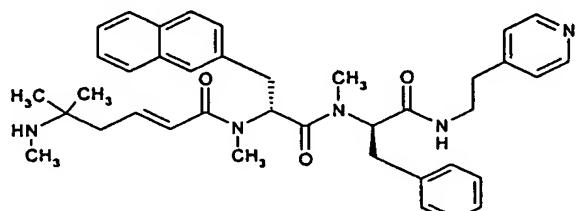
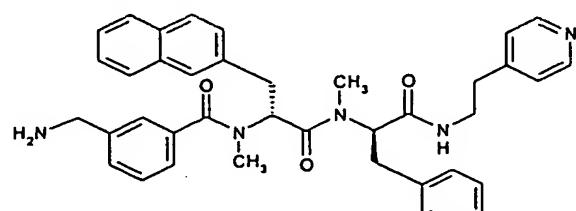
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380		646,9		
381		644,9		
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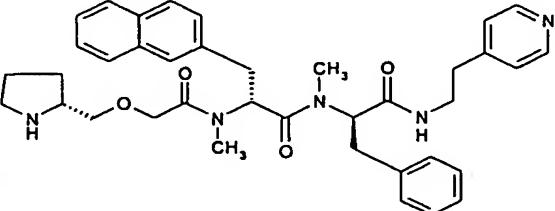
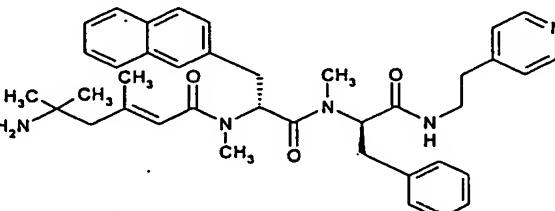
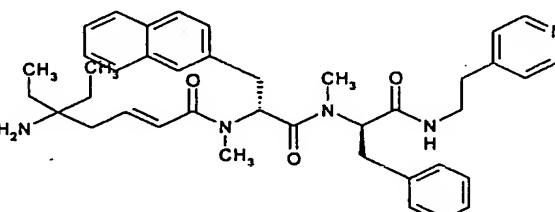
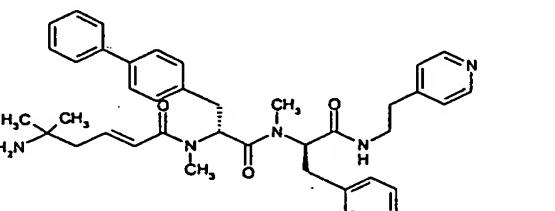
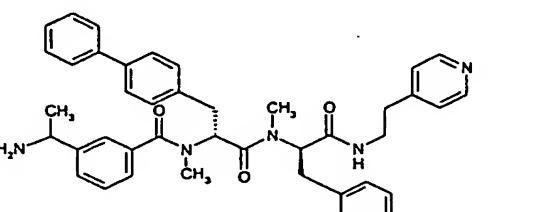
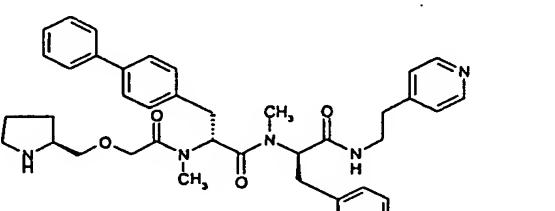
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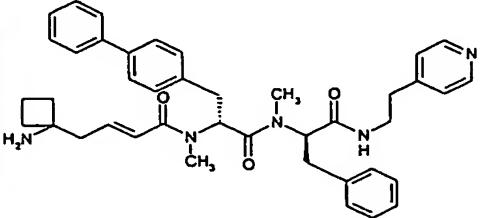
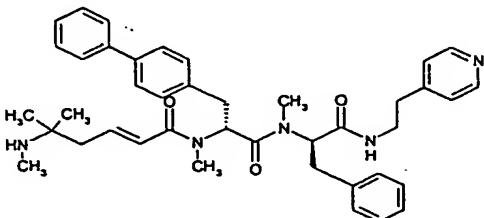
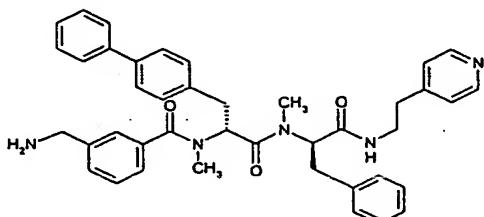
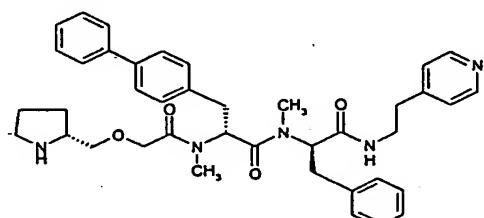
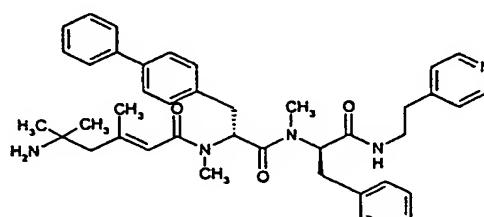
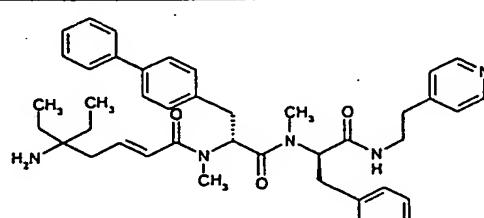
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394		639,9		
395		633,8		

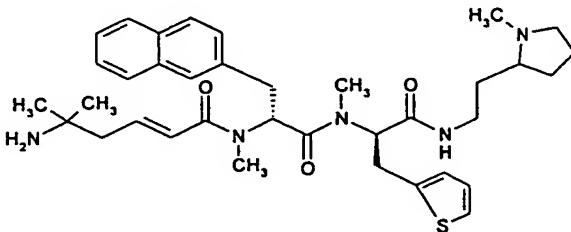
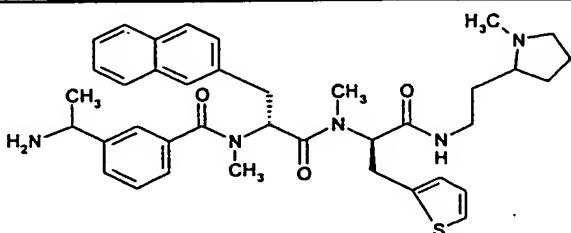
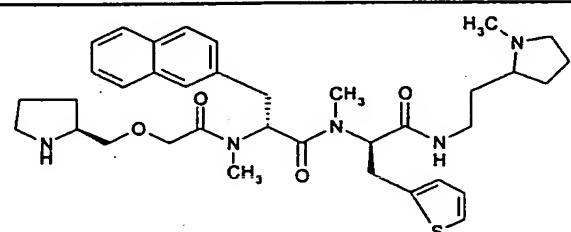
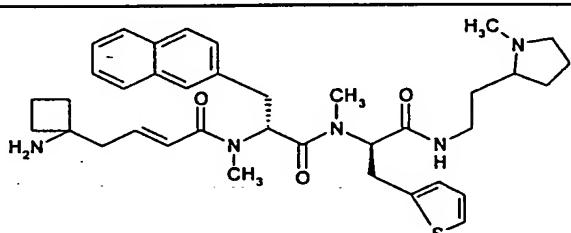
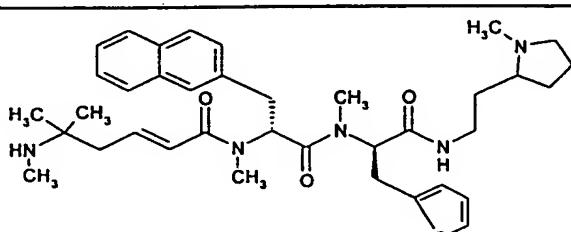
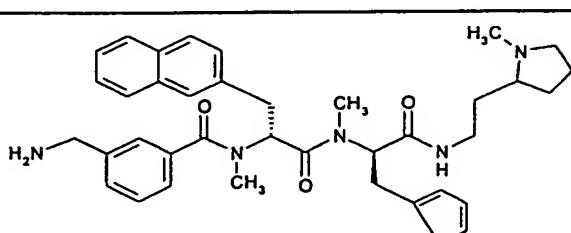
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399		651,9		
400		673,9		
401		667,9		

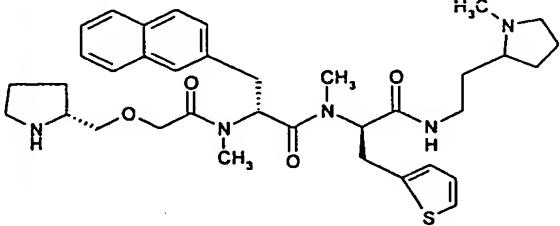
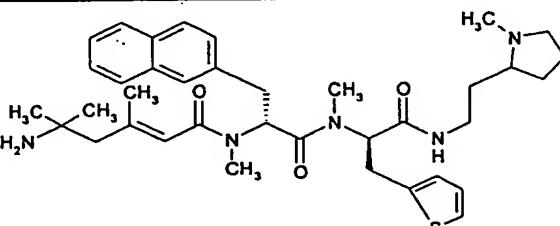
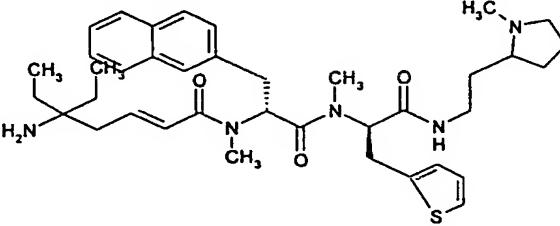
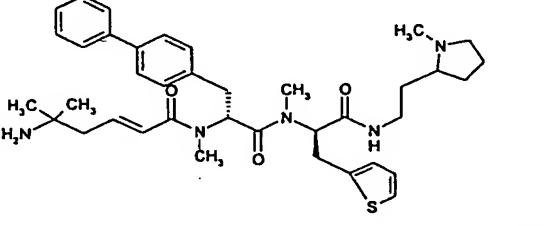
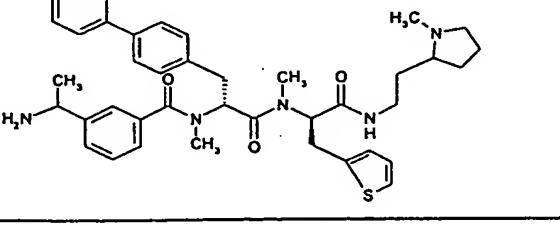
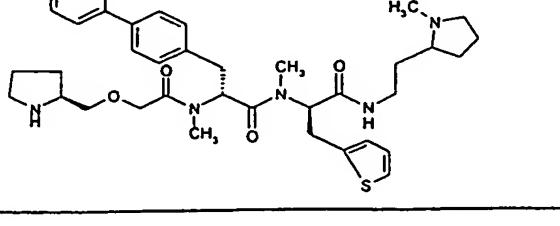
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404		659,9		
405		667,9		
406		665,9		
407		679,9		

408		619,8		
409		641,8		
410		635,8		
411		631,8		
412		633,8		
413		627,8		

414		635,8		
415		633,8		
416		647,9		
417		645,9		
418		667,9		
419		661,9		

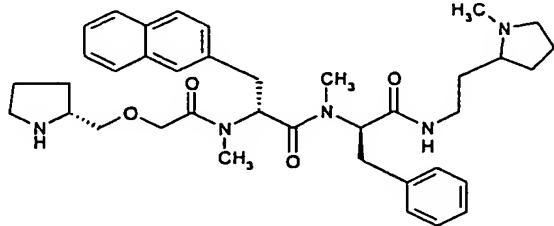
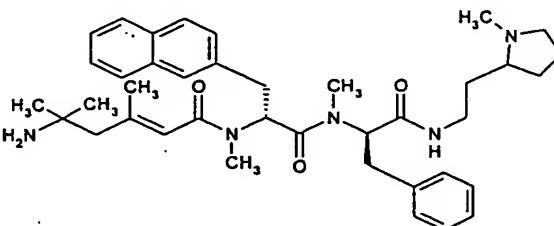
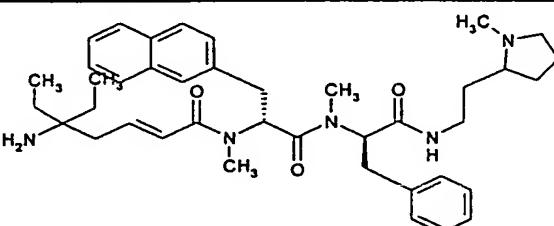
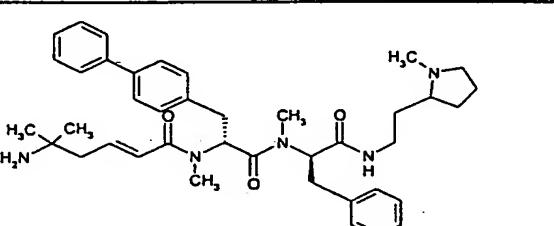
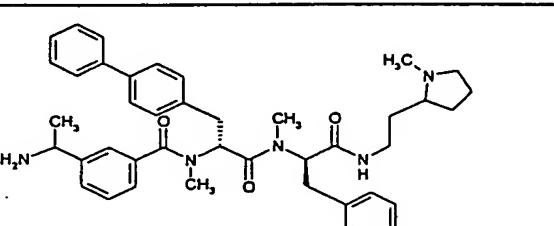
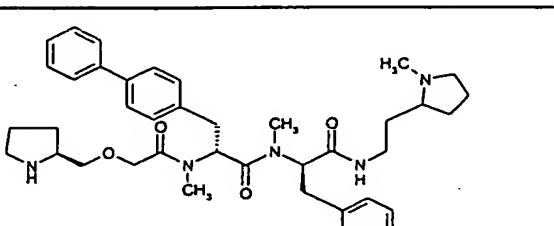
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422		653,8		
423		661,9		
424		659,9		
425		673,9		

426		631,9		
427		653,9		
428		647,9		
429		643,9		
430		645,9		
431		639,9		

432		647,9		
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434		659,9		
435		657,9		
436		679,9		
437		673,9		

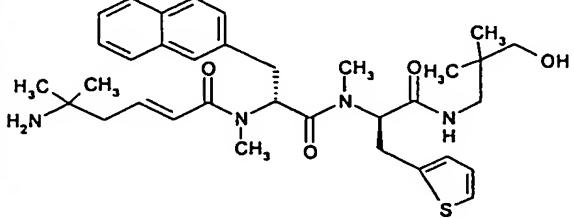
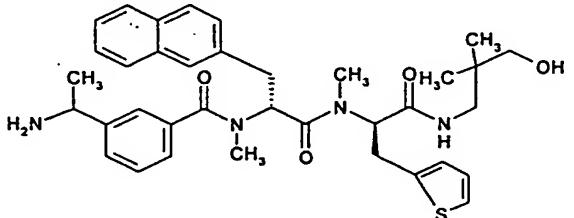
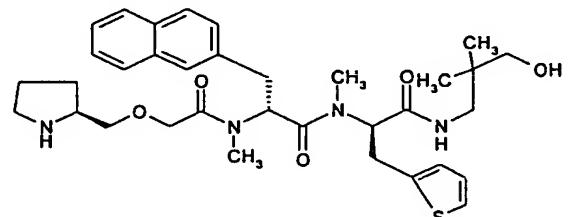
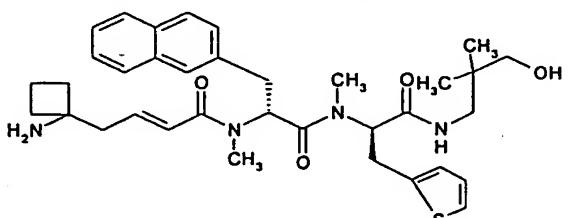
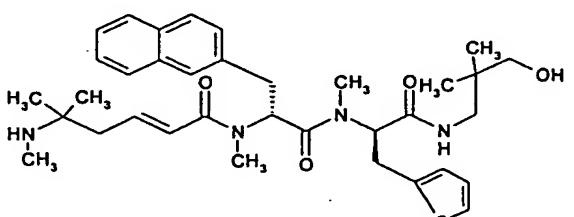
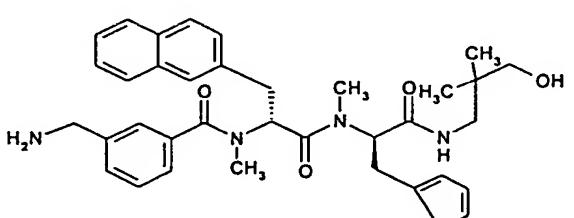
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439		672,0		
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441		673,9		
442		672,0		
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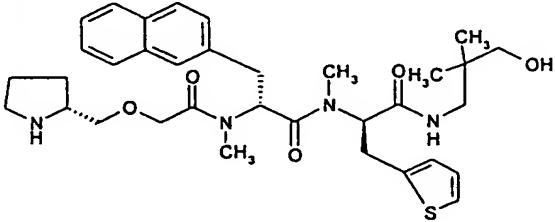
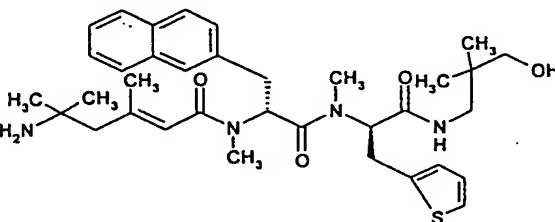
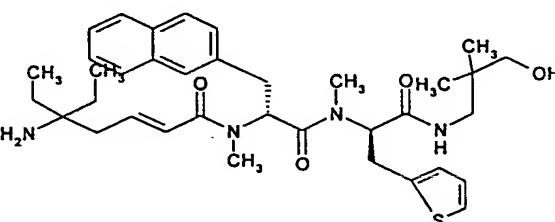
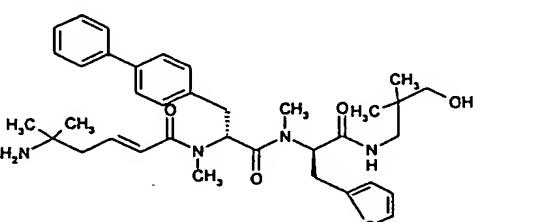
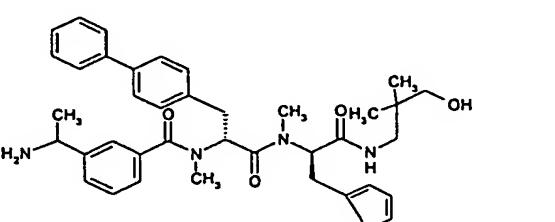
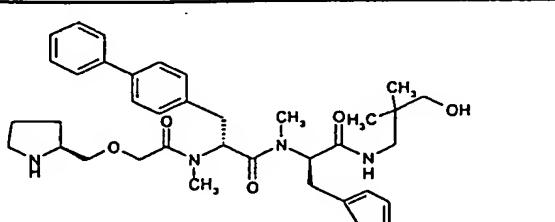
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445		647,9		
446		641,9		
447		637,9		
448		639,9		
449		633,8		

450		641,9		
451		639,9		
452		653,9		
453		651,9		
454		673,9		
455		667,9		

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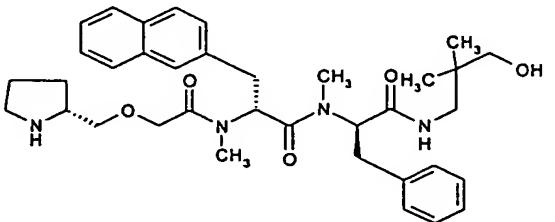
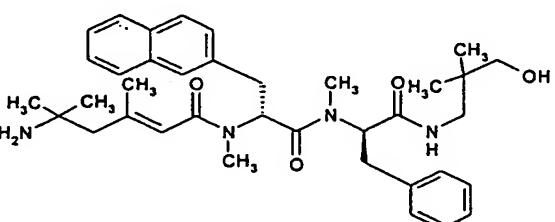
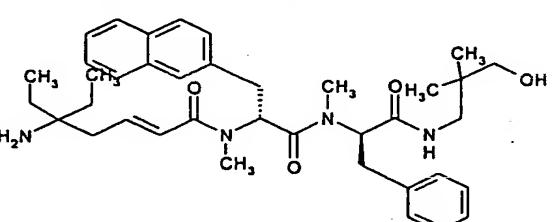
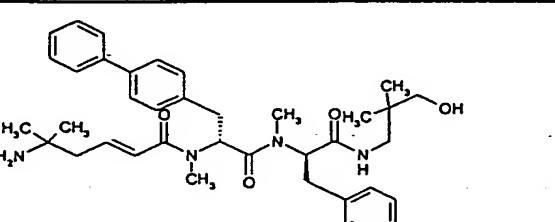
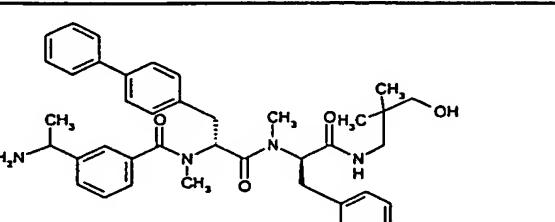
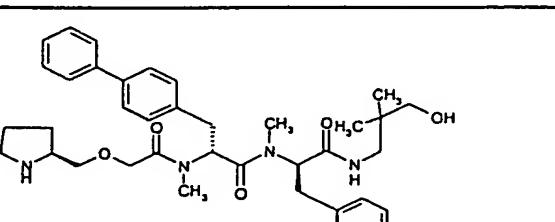
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457		665,9		
458		659,9		
459		667,9		
460		665,9		
461		680,0		

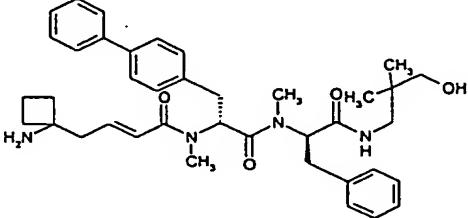
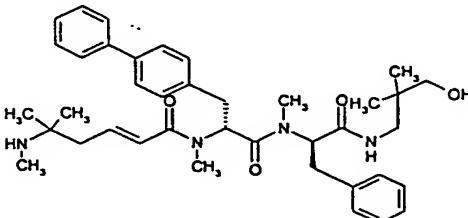
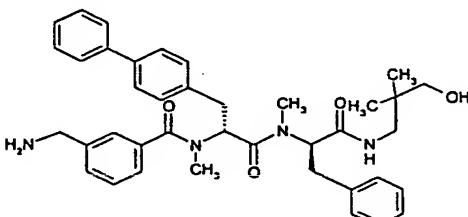
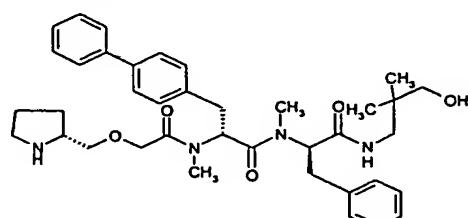
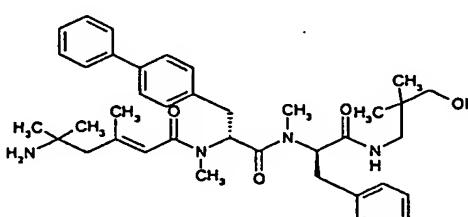
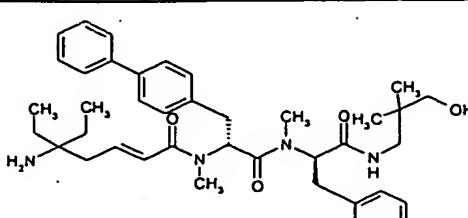
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463		628,8	
464		622,8	
465		618,8	
466		620,9	
467		614,8	

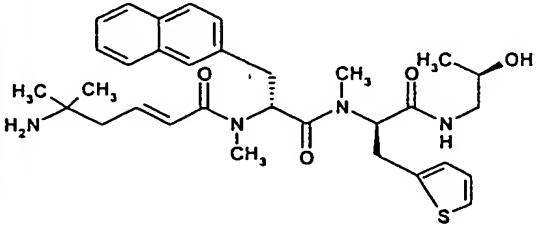
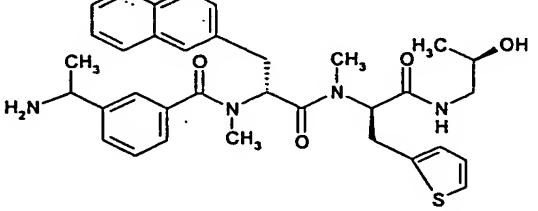
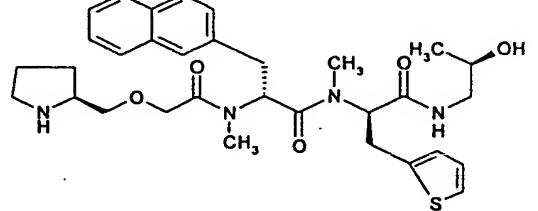
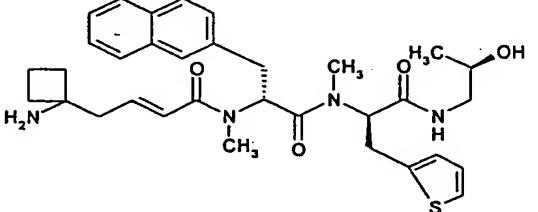
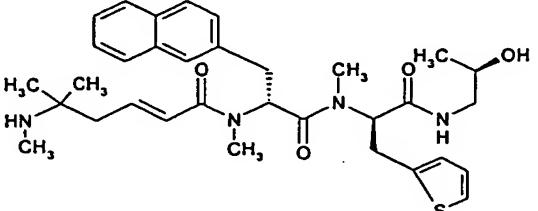
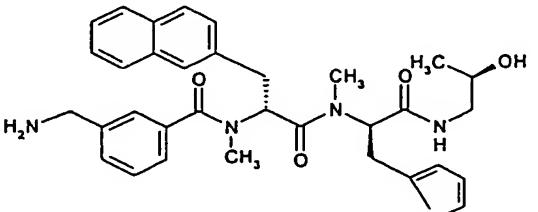
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472		654,9		
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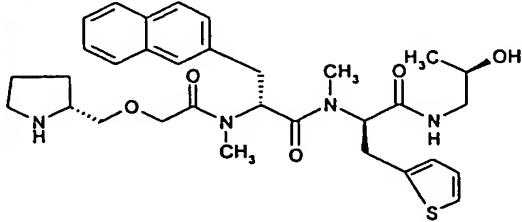
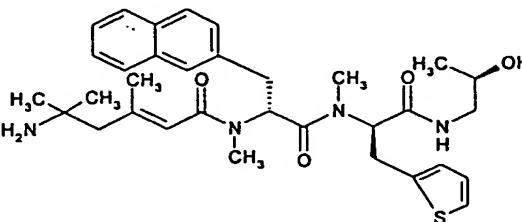
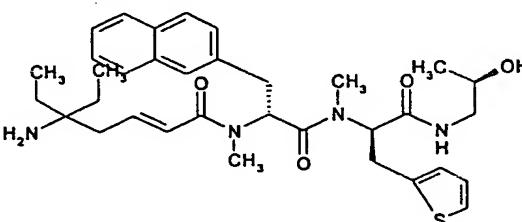
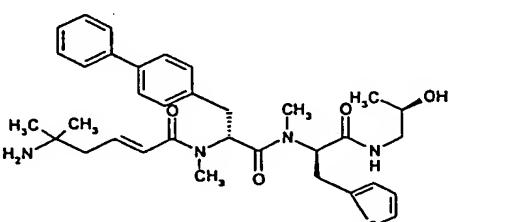
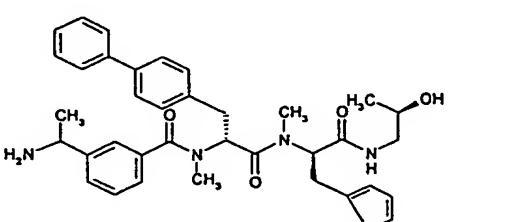
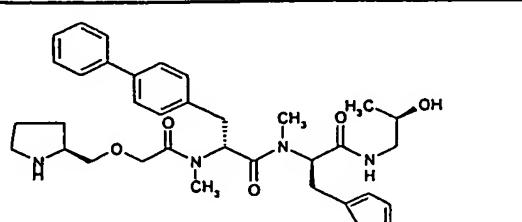
474		644,9		
475		646,9		
476		640,9		
477		648,9		
478		646,9		
479		660,9		

480		600,8		
481		622,8		
482		616,8		
483		612,8		
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485		608,8		

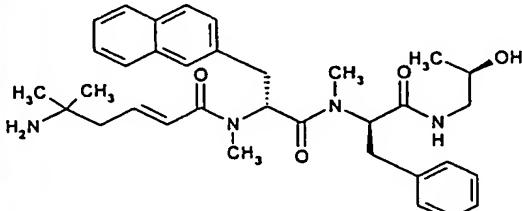
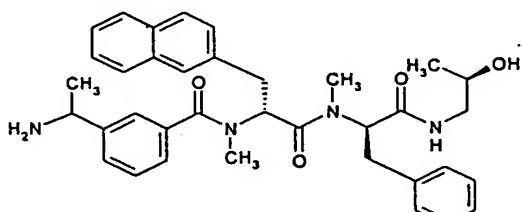
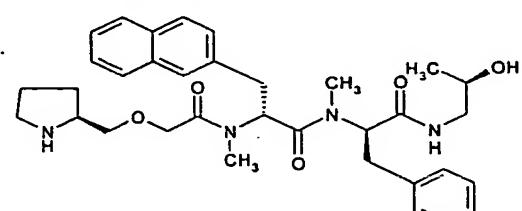
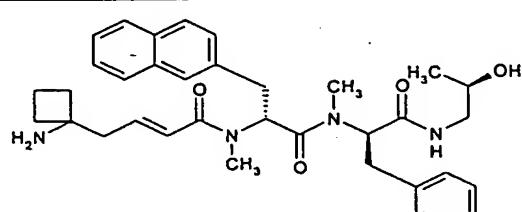
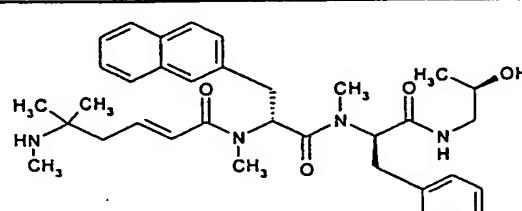
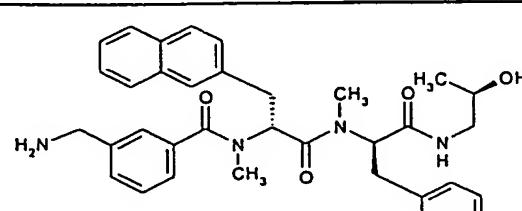
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487		614,8		
488		628,9	>	
489		626,8		
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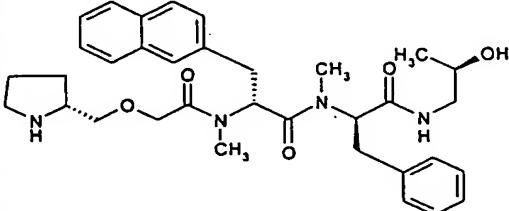
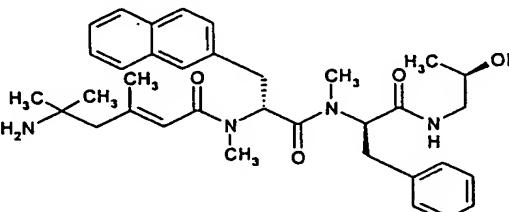
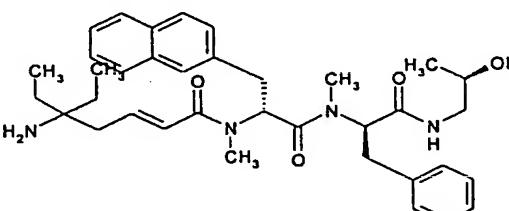
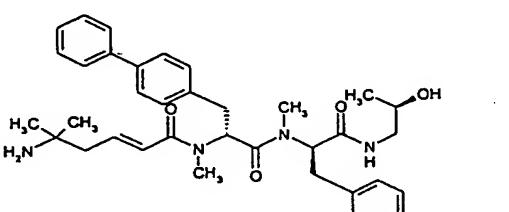
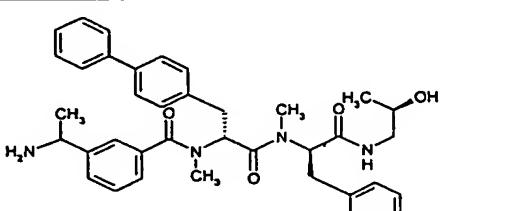
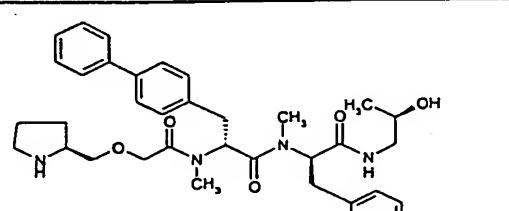
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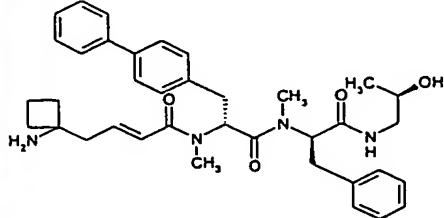
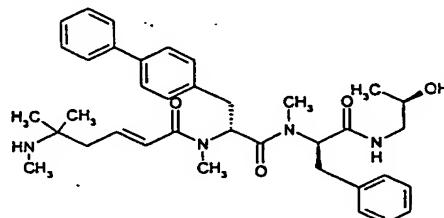
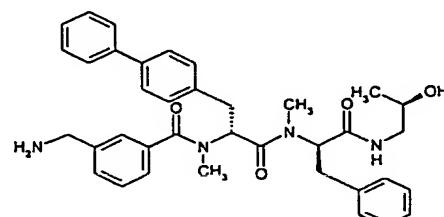
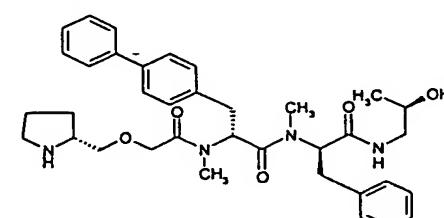
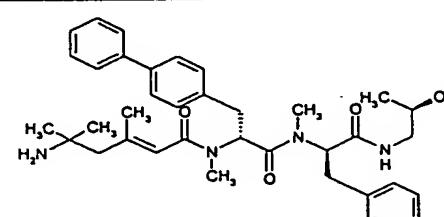
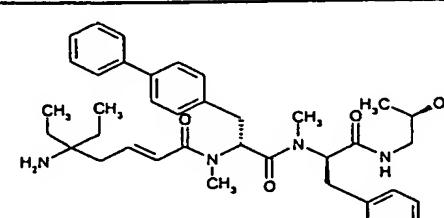
498		578,8		
499		600,8		
500		594,8		
501		590,8		
502		592,8		
503		586,8		

504		594,8		
505		592,8		
506		606,8		
507		604,8		
508		626,8		
509		620,8		

510		616,8		
511		618,8		
512		612,8		
513		620,8		
514		618,8		
515		632,9		

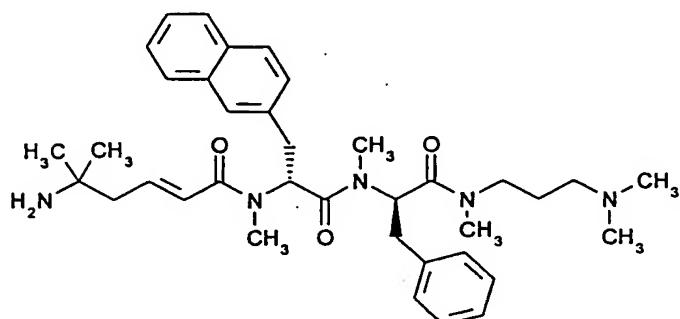
516		572,8		
517		594,8		
518		588,8		
519		584,8		
520		586,8		
521		580,7		

522		588,8		
523		586,8		
524		600,8		
525		598,8		
526		620,8		
527		614,8		

528		610,8		
529		612,8		
530		606,8		
531		614,8		
532		612,8		
533		626,8		

Example 534

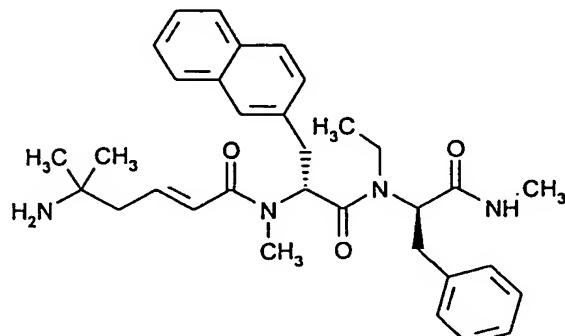
(2E)-5-Amino-5-methylhex-2-enoic acid
 N-((1R)-1-(N-((1R)-1-(N-methyl-N-(3-dimethylaminopropyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



The title compound was prepared as in example 1 using N,N,N'-trimethylpropylenediamine instead of methylamine.

Example 535

(2E)-5-Amino-5-methylhex-2-enoic acid
 N-((1R)-1-(N-((1R)-1-(N-methylcarbamoyl)-2-phenylethyl)-N-ethylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

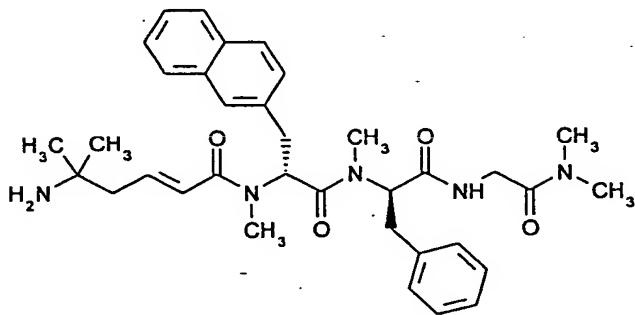


The title compound was prepared as in example 1. N-ethylation of D-Boc-phenylalanine was carried out by the use of ethyl iodide instead of methyl iodide.

5

Example 536

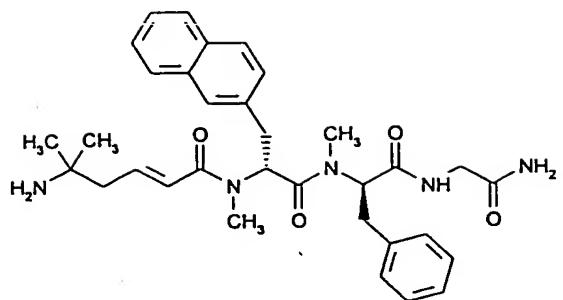
(2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-(N,N-dimethylcarbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



The title compound was prepared as in example 1 using glycine dimethylamide
instead of methylamine.

Example 537

(2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-(dimethylcarbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

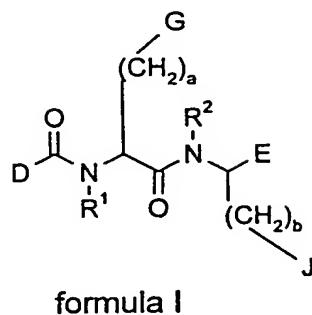


The title compound was prepared as in example 1 using glycine amide instead of methylamine.

5

CLAIMS:

1. A compound of general formula I

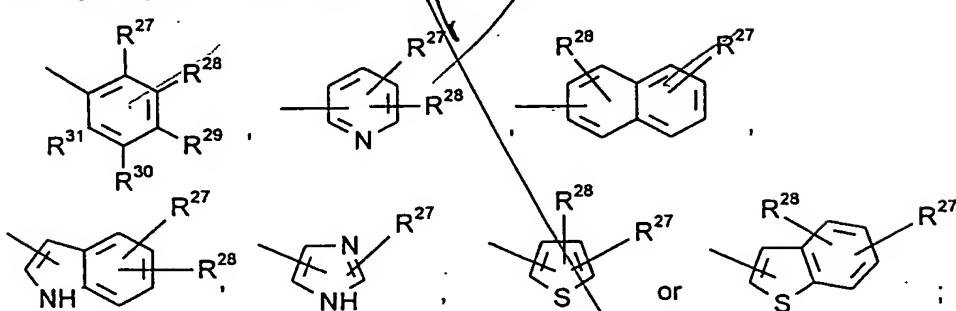


wherein

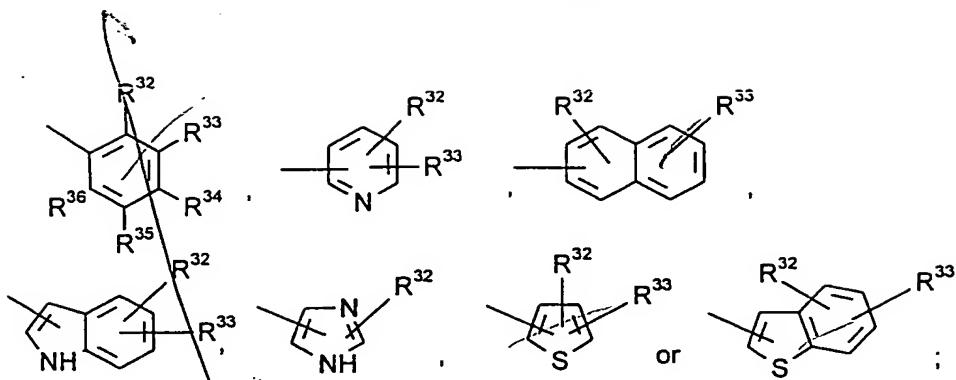
R¹ and R² are independently hydrogen, or
C₁₋₆-alkyl optionally substituted with aryl;

a and b are independently 1 or 2;

G is hydrogen, -O-(CH₂)_k-R²⁷,



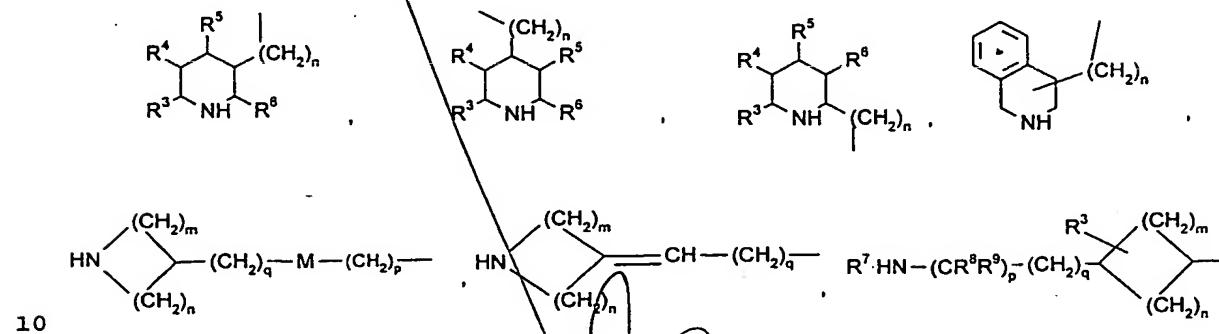
J is hydrogen, -O-(CH₂)_l-R³²,



wherein R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} and R^{36} independently are hydrogen, halogen, aryl, C_{1-6} -alkyl or C_{1-6} -alkoxy;
k and l are independently 0, 1 or 2;

5

D is



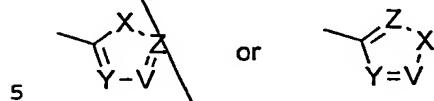
15 wherein R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are independently hydrogen or C_{1-6} -alkyl optionally substituted with halogen, amino, hydroxyl or aryl;
 n , m and q are independently 0, 1, 2, or 3;

 p is 0 or 1; M is $-CR^{11}=CR^{11a}-$, aryl, $-O-$, or $-S-$;

20 R^{11} and R^{11a} are independently hydrogen, or C_{1-6} -alkyl optionally substituted with aryl;
with the proviso that at least one of R^3 , R^4 , R^5 and R^6 is different from hydrogen,

when E is

~~-CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},~~
~~-CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴,~~
~~-(CH₂)_v-NR¹²-CO-NR¹³R¹⁴,~~



wherein

X is -N(R¹⁵)-, -O- or -S-,

V is -C(R¹⁶)= or -N=,

10 Y is -C(R¹⁷)= or -N=,

Z is -C(R¹⁸)= or -N=,

R¹⁵ is hydrogen or C₁₋₆-alkyl optionally substituted with aryl,

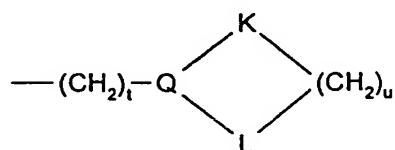
R¹⁶, R¹⁷ and R¹⁸ independently are hydrogen, -COOR¹⁹, -CONR²⁰R²¹, -

15 (CH₂)_wNR²⁰R²¹, -(CH₂)_wOR¹⁹, -(CH₂)_wR¹⁹ or halogen;

R¹², R¹³, R¹⁹, R²⁰ and R²¹ independently are hydrogen or C₁₋₆-alkyl optionally substituted with halogen, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyloxy or aryl,

20

or R¹³ is



25 wherein

Q is -CH< or -N<,

K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond,
 where R²⁶ is hydrogen or C₁₋₆-alkyl;

t and u are independently 0, 1, 2, 3 or 4;

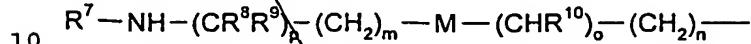
R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆-alkyl;

5 v and w are independently 0, 1, 2 or 3; or

D is



wherein R⁷, R⁸, R⁹ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

R⁷ and R⁸ or R⁷ and R⁹ or R⁸ and R⁹ optionally forming -(CH₂)_i—U—(CH₂)_j—, wherein i

15 and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

n and m are independently 0, 1, 2, or 3;

o and p are independently 0 or 1;

M is -CR¹¹=CR^{11a}-, aryl, -O-, or -S-

R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with

20 aryl,

when E is

-CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},

25 -(CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴ or

-(CH₂)_v-NR¹²-CO-NR¹³R¹⁴,

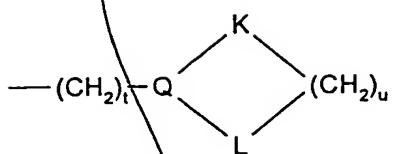
wherein

R¹² and R¹³ independently are hydrogen or C₁₋₆-alkyl optionally substituted with

30 halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl,

C₁₋₆-alkylcarbonyloxy or aryl;

or R^{13} is



wherein

5 Q is $-CH<$ or $-N<$,

K and L are independently $-CH_2-$, $-CO-$, $-O-$, $-S-$, $-NR^{26}-$ or a valence bond,

where R^{26} is hydrogen or C_{1-6} alkyl;

t and u are independently 0, 1, 2, 3 or 4;

R^{13a} is C_{1-6} alkyl substituted with aryl;

10 R^{14} is C_{1-6} alkyl;

R^{22} and R^{23} are independently hydrogen or C_{1-6} alkyl;

v and w are independently 0, 1, 2 or 3;

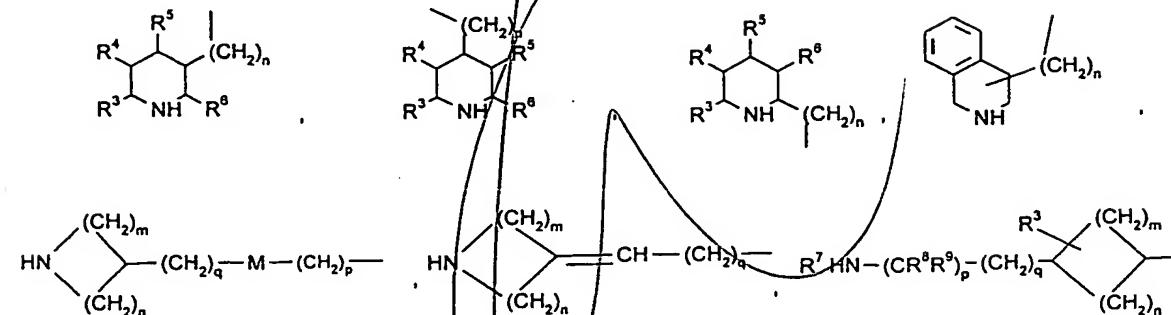
or a pharmaceutically acceptable salt thereof.

15

2. The compound according to claim 1 wherein

D is

20



wherein R^3 , R^4 , R^5 , R^6 , R^8 and R^9 are independently hydrogen or methyl;

n, m and q are independently 0, 1 or 2;

M is $-\text{CR}^{11}=\text{CR}^{11\alpha}$, aryl or $-\text{O}-$;

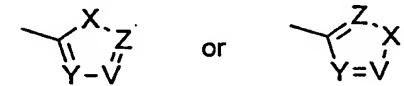
R^{11} and $\text{R}^{11\alpha}$ are independently hydrogen, or C_{1-6} -alkyl optionally substituted with aryl,

5 with the proviso that at least one of R^3 , R^4 , R^5 and R^6 is different from hydrogen, when E is

$-\text{CONR}^{12}\text{R}^{13}$, $-(\text{CH}_2)_v\text{-NR}^{12}\text{SO}_2\text{R}^{14}$, $-(\text{CH}_2)_v\text{-NR}^{12}\text{COR}^{13}$, $-(\text{CH}_2)_v\text{-OR}^{13\alpha}$,

$-\text{CH}_2\text{-OCOR}^{13}$, $-\text{CH}(\text{R}^{12})\text{R}^{13}$, $-(\text{CH}_2)_v\text{-NR}^{12}\text{-CS-NR}^{13}\text{R}^{14}$,

$-(\text{CH}_2)_v\text{-NR}^{12}\text{-CO-NR}^{13}\text{R}^{14}$,



X is $-\text{N}(\text{R}^{15})-$, $-\text{O}-$ or $-\text{S}-$,

V is $-\text{C}(\text{R}^{16})=$ or $-\text{N}=$,

Y is $-\text{C}(\text{R}^{17})=$ or $-\text{N}=$,

Z is $-\text{C}(\text{R}^{18})=$ or $-\text{N}=$,

15

R^{15} is hydrogen or C_{1-6} -alkyl optionally substituted with aryl,

R^{16} , R^{17} and R^{18} independently are hydrogen, $-\text{COOR}^{19}$, $-\text{CONR}^{20}\text{R}^{21}$, -

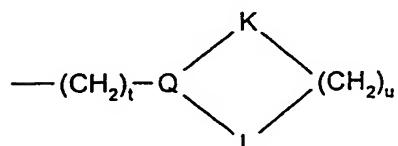
$(\text{CH}_2)_w\text{NR}^{20}\text{R}^{21}$, $-(\text{CH}_2)_w\text{OR}^{19}$, $-(\text{CH}_2)_w\text{R}^{19}$ or halogen;

20

R^{12} , R^{13} , R^{19} , R^{20} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, $-\text{N}(\text{R}^{22})\text{R}^{23}$, $-\text{CF}_3$, hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl,

or R^{13} is

25



wherein

Q is -CH< or -N<,

K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond, where R²⁶ is hydrogen or C₁₋₆-alkyl;

t and u are independently 0, 1, 2, 3 or 4;

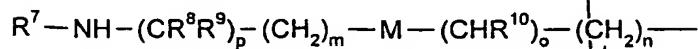
5 R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆-alkyl; and

v and w are independently 0, 1, 2 or 3.

10 3. A compound according to claim 1 wherein D is



wherein R⁸ and R⁹ are independently hydrogen or methyl;

15 R⁷ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl optionally substituted by halogen, amino, hydroxyl or aryl;

or R⁷ and R⁸ or R⁸ and R⁹ can form -(CH₂)_i-U-(CH₂)_j, wherein i and j independently are 1 or 2 and U is -O-, -S- or a valence bond;

n and m are independently 0, 1, or 2;

20 M is -CR¹¹=CR^{11a}-, aryl or -O-;

R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with aryl,

when E is

25

-CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},

-CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴ or

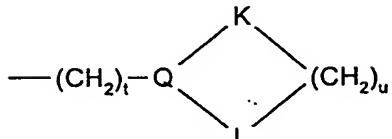
-(CH₂)_v-NR¹²-CO-NR¹³R¹⁴,

30 wherein

R¹² and R¹³ independently are hydrogen or C₁₋₆-alkyl optionally substituted with halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl,

C_{1-6} -alkylcarbonyloxy or aryl;

or R^{13} is



wherein

Q is $-CH<$ or $-N<$,

K and L are independently $-CH_2-$, $-CO-$, $-O-$, $-S-$, $-NR^{26}-$ or a valence bond,
where R^{26} is hydrogen or C_{1-6} alkyl;

10 t and u are independently 0, 1, 2, 3 or 4;

R^{13a} is C_{1-6} alkyl substituted with aryl;

R^{14} is C_{1-6} alkyl;

R^{22} and R^{23} are independently hydrogen or C_{1-6} alkyl;

v and w are independently 0, 1, 2 or 3.

15

4. A compound according to claim 1, 2 or 3 wherein D is

3-(1-aminoethyl)phenyl, 4-amino-4-ethylhex-1-enyl, (1E)-2-(azetidin-3-yl)ethenyl,
piperidin-4-ylidenyl, 2-methylpiperidin-4-yl, 2-methylpiperidin-3-yl, 2-methylpiperidin-5-yl, (1,2,3,4-tetrahydroisoquinolin-1-yl)methyl, 4-

20 aminocyclohexyl, 2-piperidylmethoxymethyl, 4-piperidyloxymethyl, 2-(2-amino-2-methylpropyl)cyclopropyl, (((2R)-pyrrolidin-2-yl)methoxy)methyl,

(1E)-4-amino-1-benzyl-4-methylpent-1-enyl, (1E)-4-amino-4-methylpent-1-enyl,

(2-amino-2-methylpropoxy)methyl, (2S)-(2-pyrrolidinyl)methoxymethyl, (2R)-(2-pyrrolidinyl)methoxymethyl, (1E)-4-amino-2,4-dimethylpent-1-enyl, (1E)-4-methyl-

25 4-(methylamino)pent-1-enyl, (1Z)-4-amino-4-methylpent-1-enyl,

(1E)-4-((2R)-2-hydroxypropylamino)-4-methylpent-1-enyl,

(2-aminobutoxy)methyl, 3-(1-aminoethyl)phenyl, 3-aminomethylphenyl, 3-(1-

amino-1-methylethyl)phenyl, 2-(1-aminocyclopropyl)ethenyl, 3-(1-

aminocyclobutyl)-1-propenyl, 3-(1-aminocyclopropyl)-1-propenyl or 2-(1-amino

cyclobutyl)ethenyl.

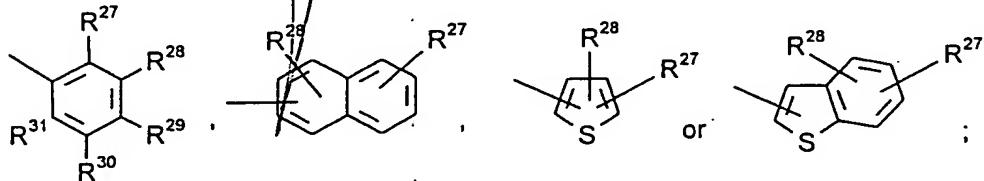
5. A compound according to claim 1, 2 or 3 wherein E is methylcarbamoyl, ethylcarbamoyl, N,N-dimethylcarbamoyl,
 5 2-methoxyethylcarbamoyl, (2S)-2-hydroxypropylcarbamoyl, (2R)-2-hydroxypropylcarbamoyl, (cyclopropylmethyl)carbamoyl, (2-(acetoxy)-2-methylpropyl)carbamoyl, phenylethylcarbamoyl, 4-pyridylcarbamoyl, (3-acetoxypropyl)carbamoyl, (3-hydroxypropyl)carbamoyl, methylsulfonylaminomethyl, ((tetrahydrofuran-2-yl)methyl)carbamoyl, 3-
 10 cyclopropylthioureido, N-methyl-N-(methylsulfonylamino)methyl, (2,2,2-trifluoroethyl)carbamoyl, cyclopropylcarbamoyl, ((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl, 3-methyl-1,2,4-oxadiazol-5-yl, methylsulfonylaminomethyl, 2,2-dimethyl-3-hydroxypropylcarbamoyl, 2-(1-methylpyrrolidine-2-yl)ethylcarbamoyl, N-methyl-N-
 15 (3-(dimethylamino)propyl)carbamoyl, N-(N,N-dimethylcarbamoyl)-N-methylcarbamoyl, N-(carbamoylmethyl)carbamoyl or 3-cyclopropylthioureido.

6. The compound according to any one of claims 1-5 wherein R¹ and R² independently are hydrogen, methyl or ethyl.

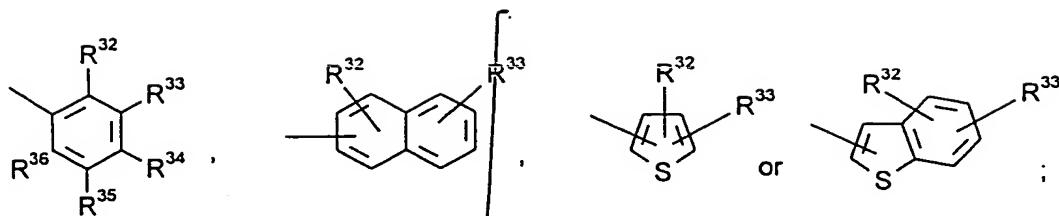
20

7. The compound according to any one of the claims 1-6 wherein a and b independently are 1.

8. A compound according to any one of the claims 1-7 wherein
 25 G is hydrogen, -O-(CH₂)_k-R²⁷,



J is hydrogen, -O-(CH₂)_l-R³²



wherein R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵ and R³⁶ independently are hydrogen, halogen, aryl, C₁₋₆-alkyl or C₁₋₆-alkoxy; and k and l are 1.

5

9. A compound according to any one of the claims 1-8 wherein R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵ and R³⁶ are hydrogen, halogen, or phenyl.

10. A compound according to claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 selected from the group consisting of

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, or the hydrochloride salt,

(2E)-3-(3-Azetidinyl)acrylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-(Piperidin-4-ylidene)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-(2-Amino-2-methylpropyl)cyclopropanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-(2-Amino-2-methylpropoxy)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-Methylpiperidine-4-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-Methylpiperidine-3-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

5 2-Methylpiperidine-5-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

10 4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(benzylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(phenethylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-(acetylamino-methyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-1-(methylsulfonylaminomethyl)-2-phenylethyl]carbamoyl}-2-(2-naphthyl)ethyl)amide,

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-((cyclopropyl-methyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

30 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-(2-methoxy-ethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((N-tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

5 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-2-hydroxy-propylcarbamoyl)-2-phenylethyl)N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(N-(3-(2-oxopyrrolidin-1-yl)propyl)carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

15 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-((2,5-dioxopyrrolidine-1-yl)methyl)-2-phenylethyl]N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide,

20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)carbamoyl)-ethyl)propionamide,

25 (2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((2-tetrahydrofuranyl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-1-(cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)-propionamide,

30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)N-methylamino)-N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide,

(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

10 (2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl
15 acetate,

(2E)-5-Amino-2-benzyl-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(1-naphthyl)ethyl)amide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide,

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-(benzo[b]thiophen-3-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)N-methylamide,

30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-3-(benzo-[b]thiophen-3-yl)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-propionamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide,

5

3-((2R)-2-(N-((2R)-2-(N-((2E)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate, or the hydrochloride salt,

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(3-hydroxy-propylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide, or the acetate salt,

15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, or the hydrochloride salt,

N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(2-piperidinyl)methoxy]acetyl]amino)-3-(2-naphthyl)propionamide,

20

4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N- methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl]-2-(2-naphthyl)ethyl)amide, or the acetate salt,

25 (2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(piperidin-4-yloxy]acetyl]amino)-3-(2-naphthyl)propionamide,

2- Methyl-piperidine-4-carboxylic acid

N-{1-[N-methyl-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl)carbamoyl]-

30 2-(2-naphthyl)ethyl} amide, or the acetate salt;

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-Hydroxypropylamino)-5-methylhex-2-enoyl)-N-

methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;

(2E)-5-Amino-N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-

5 methylcarbamoyl)-2-(2-naphthyl)ethyl)-5-methyl-N-methylhex-2-enamide;

3-(1-Aminoethyl)benzoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

10 5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2R)-2-hydroxypropylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

(4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-(((1R)-1-(1-

15 methylcarbamoyl-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(2-

20 thieryl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

(2R)-2-(N-[(2R)-2-(N-[(2-Aminobutoxy)acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide,

25 (2R)-N-Methyl-2-(N-methyl-N-((2R)-2-(N-methyl-N-(((2S)-pyrrolidin-2-yl)methoxy)acetyl)amino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionamide,

3-((2R)-2-(N-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate,

30

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-

2-(2-naphthyl)ethyl)-N-methylamide,

(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(piperidin-4-yloxy]acetyl]amino)-3-(2-naphthyl) propionamide,

5

N-Methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(2-piperidinyl)methoxy]acetyl)amino)-3-(2-naphthyl)propinamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-

10 naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-[N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl]-2-(4-

15 methoxyphenyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-[N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl]-2-phenylethyl)amide,

20

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide,

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide.

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide,

5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide,

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-

15 (2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide,

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide,

25

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide,

30 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide,

5 1-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methyl amino)-3-(2-naphthyl)propionyl-2-benzyl-4-ethylsemi-carbazide,

10 1-((2S)-2-(N-(2-(((2R)-pyrrolidin-2-yl)methoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl-2-benzyl-4-ethyl semicarbazide,

15 1-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-2-benzyl-4-ethylsemicarbazide,

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl) ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

25 (2E)-5-Methyl-5-methylaminohex-2-enoic acid
N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenyl ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-3,5-dimethylhex-2-enoic acid
N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) amide,

(2E)-5-Amino-5-methylhex-2-enoic acid
N-methyl-N-((1R)-1-(N-methyl-N-(2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide,

30 5-Amino-3,5-dimethylhex-2-enoic acid

N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

(2E)-5-Amino-5-methylhex-2-enoic acid

5 N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Methyl-5-methylaminohex-2-enoic acid

10 N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Methyl-5-amino-5-methylhex-2-enoic

acid-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thien-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

15

5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-2-(3,4-difluorophenyl)-1-methylcarbamoylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

20 5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-2-phenyl-1-ethylcarbamoylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-

25 2-hydroxypropylcarbamoyl)-2-(3,4-difluorophenyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

5-Amino-5-methyl-hex-2-enoic acid

(1-[{2-(2-fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl}-2-(2-naphthyl)eth

30 yl)methylamide,

(2Z)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

5 (2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-3-(2-naphthyl)propionamide,

10 (2R)-2-(N-[{2-Amino-2-methylpropoxy}acetyl]-N-methylamino)-N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide,

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide, and its acetate salt;

15 (2E)-5-Amino-5-methylhex-2-enoic acid
N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

20 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-2-(3,4-difluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

25 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

(2E)-4-(1-Aminocyclobutyl)-but-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide;

30 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(2-

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naphthyl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

5

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

10 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

15 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

20 3-(1-Aminomethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

30

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-

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y!)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-

5 (benzo[b]thiophen-3-yl)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

10

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-

15 (methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

30

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

5 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

10 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

15 (2E)-5-Amino-5-methylhex-2-enoid acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;

20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

25 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

5

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

10 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-

15 N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

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3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

5 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

10 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

20 15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

25 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;

35 30 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-

yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

5

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
10 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-
yl)propion-amide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;

20

3-(1-Aminoethyl)-N-methyl-N-((1*R*)-1-(N-methyl-N-((1*R*)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

25 2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-(1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

30 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

5 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

10 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

30 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide;

35 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)-

propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propion-
5 amide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-naphthyl)-ethyl)amide;

10

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

15

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

20

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

25

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

30

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-

(benzo[b]thiophen-3-yl)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-

5 (benzyloxy)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

10 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-

15 (benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(biphen-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

30 2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

5 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

10 (2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide;

15 (2E)-5-Amino-5-methylhex-2-enoic acid
N-((1R)-1-(N-((1R)-1-(N-methyl-N-(3-dimethylaminopropyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

20 (2E)-5-Amino-5-methylhex-2-enoic acid
N-((1R)-1-(N-((1R)-1-(N-methylcarbamoyl)-2-phenylethyl)-N-ethylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide; or

25 (2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-(dimethylcarbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide; or

or a pharmaceutically acceptable salt thereof.